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Newer Concepts of Alcoholism and Its Treatment

A Symposium Presented by
The Colorado Academy of General Practice
Denver, Colorado, 25-26 May 1961

EBBE CURTIS HOFF, Ph.D., M.D., Special Editor

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Editorial and Bibliographic Note

Background

This special Supplement consists of nearly all the papers presented at a symposium entitled "Newer Concepts of Alcoholism and its Treatment," held on 25 and 26 May 1961 at Denver, Colorado. A complete table of contents appears on page v.

The symposium was presented by the Colorado Chapter of the American Academy of General Practice with the aid of a grant from the Roche Laboratories Division of Hoffmann–La Roche, Inc. The program was approved for 15 hours of Category 1 credit by The American Academy of General Practice. *Chairman* of the symposium was Leonard Goldberg, M.D., Director of the Department of Alcohol Research, Karolinska Institutet, Stockholm, Sweden. *Chairmen* of the several sessions were Marvin Block, M.D., Chairman of the Committee on Alcoholism of the American Medical Association; Edward Delehanty, M.D., Chairman of the Colorado Commission on Alcoholism; Dr. Leonard Goldberg; and Norbert L. Shere, M.D., Chairman of the Committee on Alcoholism of the Colorado State Medical Society. Other participants, in addition to those whose papers are published herein, included Dale M. Hathaway, M.D., President of the Colorado Academy of General Practice, and Ian Kent, M.D., Medical Director of the National Committee for Education on Alcoholism, Province of Quebec.

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The Pharmacology of Alcohol Intoxication

H. Kalant, M.D., Ph.D.[1]

THE PHARMACOLOGICAL INVESTIGATION of any drug presents a multitude of problems which do not always appear to be obviously related to the therapeutic use of the drug. These problems include the absorption, distribution and metabolism of the drug; the mechanism of its action; dose–response relationships; lethal dose; and mechanism of toxicity. Normally, therefore, the pharmacologist examines the effects of a drug in at least two dose ranges: the low or medium dose range in which the desired therapeutic effects are achieved and the high dose range in which toxic or lethal effects appear. In the case of alcohol, a third dose range must be considered, a very low one in which the doses consumed are so small that the alcohol is metabolized without ever reaching blood levels high enough to produce detectable physiological effects. This is the range in which alcohol is used as a foodstuff, and is the range in which most experimental work concerning the nutritional effects of alcohol has been carried out.

It would be impossible even to begin to deal with all these problems in the present paper. Fortunately, it is quite unnecessary to try. The absorption, distribution and metabolism of ethyl alcohol are well covered in recent textbooks and reviews (1–5), and more recent investigations with C^{14}-labeled alcohol (6–9) have confirmed and extended earlier work. Koppanyi and his co-workers have described the lethal-range effects (10). This discussion, therefore, will be limited to the acute effects of alcohol, in what we may consider, for convenience in reference, as the "therapeutic" range. This differentiation is perhaps worth emphasizing again. Most people who drink alcohol do so neither with the thought that it is a source of vitamin-free calories, comparable to sugar or starch, nor with the intention of committing suicide. Most voluntary human con-

[1] Assistant Research Director (Biological Sciences), Alcoholism and Drug Addiction Research Foundation, Toronto, Ontario.

sumption of alcohol is either a manifestation of sociability, or an attempt to produce a therapeutic effect consisting of a feeling of pleasure or relief from distress. In the course of this, some undesired side effects, such as dizziness, impaired motor coordination and sleepiness, may occur but these side effects do not necessarily have anything to do with the serious toxic effects which can produce death from alcohol poisoning. This differentiation appears to have been ignored by many investigators who have studied the pharmacology of alcohol. Massive near-lethal doses have been given in some experiments, yet the findings have been discussed as though they were necessarily applicable to the milder degrees of intoxication which human beings usually produce in themselves. If this pitfall is avoided, we may avoid some of the confusion surrounding the problems likely to be faced by the physician in attempting to treat the alcoholic patient.

Effects of Alcohol on Living Cells

Ethyl alcohol is one of a homologous series of compounds with many similarities in their physical properties, metabolic fates and pharmacological effects. In general, the immediate acute toxicity of this series of alcohols increases with increasing molecular weight, methyl alcohol being the least toxic, ethyl alcohol somewhat more so, propyl still more, and so on. This applies not only to toxicity in the whole animal but to such diverse manifestations as inhibition of respiration of brain tissue, killing of bacteria and inhibition of respiration of unicellular organisms. On the other hand, the solubilities decrease progressively with increasing molecular weight, so that the higher alcohols become too insoluble to reach a serious toxic concentration. In the special case of methyl alcohol, there is an additional delayed toxicity due to the formation of formaldehyde and formic acid by the oxidation of methanol. This feature, which gives rise to severe acidosis, coma and blindness, is actually a different problem from that of the acute intoxication produced by the methyl alcohol itself, which is in fact considerably milder than that produced by ethyl alcohol. While the special toxicity of methyl alcohol and the potent toxicities of the higher alcohols are well known to the medical staffs of hospital emergency departments and to the police, most people know enough to avoid exposure to these substances. Small amounts of higher alcohols, present as congeners in most whiskies and other distilled beverages, may con-

ceivably play some part in the over-all intoxicating effects of these beverages, including the well-known problem of the hangover. However, most of the pharmacological problems faced by the consumer of alcohol and by the physician who treats him are due principally to the effects of ethyl alcohol.

It long been known that ethanol, in sufficient concentration, is toxic to all types of living cells and it is widely used as a germicide. It is also used by injection to kill nerve cells in the treatment of intractable pain. Biologists have studied its so-called "narcotic" effect on the respiration of sea urchin eggs and other unicellular organisms. Like a chemical Frankenstein ethanol is even toxic to the yeast which produces it. In higher animals the depressant actions of alcohol have been demonstrated not only in the intact subject but on isolated tissues of all types. All these effects of ethanol, however, may be of relatively little value in explaining the usual phenomena of alcohol intoxication in the human, for two reasons: (*1*) All of the mentioned effects are produced by concentrations of ethanol in excess of those which produce mild to moderate intoxication in man, and many require alcohol concentrations far in excess of those compatible with life. (*2*) The degree of intoxication produced in the living subject depends not only on the concentration of alcohol reached in the blood and tissue fluids, but also on the rate at which it is reached. Numerous investigators have found that a subject is much more intoxicated at a given blood alcohol concentration if it is reached rapidly than if it is reached slowly (11, 12, 13); and he is much less intoxicated at a given concentration during the decline in blood alcohol level after the peak is passed than during the early phase of rising blood alcohol level. The nervous system has the ability to adapt to the presence of alcohol, so that symptoms appear to depend at least as much upon a change in alcohol concentration as upon the actual presence of alcohol. For this reason an experiment in which a rat is given 6 g. of ethanol per kg. of body weight by intraperitoneal injection (equivalent on a weight basis to 1,300 ml. of whisky in a single dose to an average man) must not be assumed to produce the same effects as a quart of whisky consumed by a man over a period of 12 to 24 hours. It is doubtful indeed whether the pattern of acute intoxication, by amounts of alcohol compatible with life, ever affects demonstrably and directly anything but the nervous system, and possibly the liver.

Effects of Alcohol on the Liver

There can be no question concerning the indirect nutritional effects of chronic excessive intake of ethanol. Alcohol is oxidized to acetaldehyde by an enzyme, alcohol dehydrogenase, which to all practical purposes is found only in the liver. Unless its metabolism is blocked, as by disulfiram[2] or citrated calcium carbimide,[3] the acetaldehyde is subsequently converted to acetylcoenzyme A, a key substance which can be used in the synthesis of fats, nonessential amino acids and carbohydrates, or can be oxidized via the tricarboxylic acid cycle to yield energy, carbon dioxide and water. Acetyl-CoA derived from alcohol is indistinguishable from that derived from other foodstuffs. Alcoholic beverages, however, do not provide adequate amounts of vitamins, minerals or other dietary requirements. For this reason the nutritional significance of alcohol is virtually indistinguishable from the nutritional significance of refined sugar, starch or pure saturated fatty acids. If too large a proportion of the total caloric intake is derived from any one of these substances the inevitable consequence is a deficiency of essential amino acids, vitamins and other nutritional requirements which are normally provided in a balanced diet. One of the common consequences of such imbalance, as is now well known, is the accumulation of fat in the liver, due to a deficiency of choline and other lipotropic factors (14). Experimentally the same type of result could be produced with equal ease whether cane sugar or alcohol were the cause of the nutritional imbalance. Clinically, many other signs of vitamin deficiency were formerly associated with the picture of alcoholism, and presumably for the same reason. Since a human being can theoretically derive more than 2,000 calories in 24 hr. from continuous oxidation of alcohol at maximum normal rates, it is easy to see why the ingestion of other foods, with their essential ingredients, may be seriously diminished. For this reason such pictures of vitamin deficiency as beri-beri, peripheral neuropathy and Wernicke's syndrome were long known as the "wages of sin" for the alcoholic (15). With the supplementation of flour, cereals and other foods by vitamins, many of these features of alcoholism have disappeared in recent years. The fatty liver, however, is still very much a part of the picture and has been amply confirmed by punch biopsy in alcoholic patients (16). Whether

[2] Antabuse, Ayerst.
[3] Temposil, Lilly.

this is the cause of portal cirrhosis in alcoholics, however, is a separate question (17, 18, 19). To deal with this problem here would lead too far afield from the subject of the present review.

The question of a direct action of alcohol itself upon the liver is a matter of active debate. It is common medical practice to refer to alcohol as a hepatotoxic substance and to forbid its use in the presence of liver disease, though the evidence for this view is in fact sparse and not convincing. It has been shown repeatedly that a well-nourished, normal, healthy animal, given a single intoxicating dose of alcohol, shows a substantial increase in liver fat detectable within a matter of 4 to 6 hr. and maximal within 12 to 18 hr. (20–23). This accumulation of liver fat occurs only in the presence of adrenocortical and anterior pituitary hormones, being prevented or abolished in rats from which these glands are removed (20). Gas chromatographic analysis of the fat which accumulates in the liver under these conditions has established beyond doubt that it comes chiefly from peripheral fatty tissues and is carried to the liver rather than being produced there (22, 23). The evidence, therefore, does not establish clearly whether alcohol can be considered to be a directly hepatotoxic substance rather than simply a cause of malnutrition. Other types of evidence on this subject are sparse and rather contradictory. It has been shown that in patients recovering from prolonged alcoholic bouts a single small dose of alcohol is capable of causing an abrupt rise in the serum levels of glutamic–oxalacetic and glutamic–pyruvic transaminases (24, 25). After 2 weeks or more on a good diet the same patients no longer showed a rise in serum enzymes with the same dose of alcohol. This finding suggests that small doses of alcohol in a healthy well-nourished subject are not hepatotoxic. On the other hand, small doses of alcohol have been reported to produce significant disturbances in the galactose tolerance test, both in normal and in alcoholic subjects (26–29). In summary, the evidence concerning acute effects of alcohol upon a previously healthy liver is at present inadequate to permit any conclusion about the possibility of effects other than nutritional ones.

Effects of Alcohol on the Nervous System

The nervous system, therefore, must necessarily occupy most of the attention of the pharmacologist concerned with the mechanism of acute alcohol intoxication. Even here, however, there is difficulty

in merely defining the problem, let alone proposing a correct answer. It has not yet been established whether alcohol in low or moderate dosage produces demonstrable effects by direct action upon all parts of the nervous system, or whether its many effects are produced via a primary action upon a fairly restricted area of the central nervous system. Investigation of the effects of alcohol upon complex functions, such as performance tests of various types and reaction times to visual or auditory stimuli, are of little help. If a subject is required to press a button every time he sees a red light flash, or to decide between button *A* and button *B* depending upon whether a red or a green light flashes, his final response depends upon a complex chain of sensory perception, mental recognition of the stimulus, choice of appropriate action, recognition of the appropriate button and actual motor performance of the button-pressing. Any or all of these components could conceivably be either stimulated or depressed by alcohol, and all components need not necessarily be affected in the same way. It is not surprising, therefore, that results of studies of reaction time as affected by alcohol have been highly varied and contradictory (30). A most interesting report of the influence of low doses of alcohol on automobile driving (31) suggests that the effects vary according to whether the subject is basically introverted or extroverted. The introvert becomes exceedingly cautious, driving very slowly and meticulously, while the extrovert becomes reckless, driving rapidly and with poor control. It is obvious, then, that the responses to alcohol in the performance of a complex task depend upon many factors, and that an explanation of the action of alcohol must be built up from studies of simpler components of nervous function.

Effects on Peripheral Neurones and Reflex Arcs

The simplest components are individual peripheral motor neurones and simple spinal reflex arcs. Numerous investigations of alcohol effects on these components have been carried out but the results are contradictory. The simplest approach consisted of exposure of the sciatic nerve in the frog (32, 33), with measurement of membrane potentials and impulse transmission before and after local application of alcohol. It was found that weaker alcohol solutions, about 0.5 per cent, caused an increase in local excitability of the nerve while stronger solutions or longer times of exposure caused a fall in excitability, with nerve block. Even the lowest concentra-

tions used, however, were very high indeed in terms of blood alcohol concentrations; and the exposed nerves could hardly be considered physiologically normal. Physiologically less objectionable methods, such as measurement of the excitability of motor nerves in terms of their chronaxie or rheobase (34–42), or of the latent period and magnitude of tendon reflexes (43–46) have yielded apparently contradictory results. Some of the contradictions have undoubtedly arisen because different investigators have used different doses of alcohol, different rates and routes of administration and different times of observation. In general, however, alcohol tends to abolish the normal differences in motor chronaxie between the nerves to flexor and extensor muscles; and the chronaxies in many cases show an initial drop, indicative of greater excitability of the nerves. With more profound intoxication the excitability tends to decrease. Similarly, simple spinal reflexes have been reported to show an initial increase in speed or amplitude on administration of alcohol, with a later decrease during deeper levels of intoxication. These results do not necessarily reflect a direct action of alcohol on the peripheral neurones concerned. It is well known that higher levels of the central nervous system exert selective stimulatory and inhibitory influences upon synaptic transmission between the neurones involved in spinal reflexes. The change in reflexes and in motor nerve chronaxie, therefore, may reflect an effect of alcohol upon these central regulatory influences rather than a direct effect of alcohol upon the peripheral neurones. An attempt is currently being made[4] to resolve this problem by measuring the effects of single doses of 1½ and 4½ oz. of whisky upon conduction velocity in the ulnar nerve, as determined electromyographically (47) in healthy conscious subjects. Since the function measured does not involve synaptic transmission, but only conduction within the axone, it is greatly to be hoped that this study will remove the confusion arising from earlier work.

Relatively simple reflexes involving the brain stem rather than the spinal cord have also been found to be modified by alcohol in a way which suggests primary action upon some central regulatory system rather than upon the reflexes themselves. For example, certain types of sudden noise cause a reflex twitch of the guinea pig's ear. Small doses of alcohol have been found to increase this reflex twitch, while larger doses abolish it (48). Stimulation of the

[4] BASMAJIAN, J. V. [Personal communication.]

vestibular apparatus electrically, or by hot or cold water, results in nystagmus. It has been reported that moderate alcohol intoxication, with peak blood alcohol levels of 150 mg. per 100 ml., lowers the latency period for nystagmus produced by cold stimulation of the labyrinth (49). The threshold for production of nystagmus by electrical stimulation has also been reported to be decreased by low doses of alcohol and raised by higher ones (50), although it must be admitted that not all investigators agree upon this (38–41, 51–56). Finally, quite small doses of alcohol have been shown to produce a phenomenon known as positional alcohol nystagmus. This phenomenon, though described by earlier investigators (57, 58, 59), has been most thoroughly and elegantly studied by Aschan and Goldberg and their collaborators (60–63). Positional alcohol nystagmus may be considered a fairly simple brain-stem reflex: the sensory stimulus is gravitational pull upon the receptors in the vestibular apparatus, the afferent is the vestibular nerve, the internuncial neurone is that from the vestibular nucleus to the oculomotor nuclei, and the motor efferents are the oculomotor, trochlear and abducens nerves to the external ocular muscles. Alcohol might therefore provoke the nystagmus response to gravitational stimulation either by increasing the sensitivity of the primary reflex arc, or by removing some higher inhibitory influence. By analogy with the lower reflexes mentioned above, and in view of the very abundant nervous connections between the vestibular nuclei and the reticular structure of the brain stem, it seems much more likely that alcohol acts primarily to remove higher inhibitory influences.

In summary, then, the studies of alcohol effects upon simple reflexes and peripheral neurones, while by no means complete or conclusive, suggest that alcohol, in moderately intoxicating concentrations, acts primarily upon central regulatory mechanisms which affect the reflexes secondarily.

Effects on the Cerebral Cortex

The signs and symptoms of alcohol intoxication which have been known since antiquity are chiefly those relating to behavior—a feeling of relaxation, impairment of judgment, loss of emotional restraint, slurring of speech and numbing of sensation, and so on, until stupor, and finally coma, supervene. For this reason the classical view of alcohol intoxication was one of progressive depression

affecting first the most highly developed portion of the brain, namely, the cerebral cortex. Thus alcohol was assumed to act first to depress critical faculties and reasoning power, leading to the patterns of behavior which all recognize as drunkenness. In higher doses it was thought to depress successively lower levels of the brain, from the cortex through the thalamus, ultimately to the vital centers of the medulla.

Attempts to explain such an assumed primary depression of the cortex have been mainly biochemical in outlook. Perhaps by analogy with the so-called "narcotic" effect on simpler organisms, many investigators have sought evidence of an impairment by alcohol of oxidative metabolism in the cerebral cortex. Unexpectedly, earlier investigators found that alcohol in concentrations of 2 per cent or less increased the respiration of brain cortex slices in vitro, and that depression of respiration did not occur until concentrations of 4 per cent or more were employed (64–67). When the brain slices were stimulated by the addition of potassium chloride (66, 68, 69) or by electrical pulses (70), however, alcohol did exert a depressing action at concentrations as low as 0.2 per cent. However, it should be noted that signs of alcohol effect in humans can begin at blood alcohol levels as low as 0.03–0.04 per cent, and are quite marked at a level of 0.2 per cent. Moreover, various studies of cerebral circulation and cerebral metabolism in living human subjects (71–74) have failed to show any effect of alcohol on cerebral blood flow or oxygen uptake except at alcohol levels sufficient to produce coma. These results are hardly in keeping with the concept of a primary depression of metabolism of the cerebral cortex by alcohol.

Direct recordings of electrical potentials from the cerebral cortex have likewise failed to support the idea of primary depression by alcohol. Various investigators have found that intravenous or oral administration of ethanol in low or moderate dosage caused a decrease in threshold for local electrical excitation of the cerebral cortex—i.e., an increase in excitability—and that decrease in excitability did not occur until very large doses of alcohol were given (75, 76). A most elegant demonstration of this relationship was reported recently (77), in which indwelling semimicro electrodes were placed in various parts of the brain and the animals allowed to recover. It was shown that in the fully conscious normal animal the first effects of alcohol on the cerebral cortex were an increase

in large-amplitude electrical activity and a decrease in the threshold for direct local electrical excitation of the cortex. Only at much higher blood alcohol levels did a decrease in electrical activity and excitability of the cortex occur.

Neither the biochemical nor the neurophysiological evidence, therefore, supports the idea that alcohol acts primarily and directly upon the cerebral cortex. We must consider the probability that alcohol acts first upon some regulatory structure which modifies the activity of the cerebral cortex as well as that of the peripheral neurones and the spinal and brain-stem reflexes. Modern neurophysiology has identified this regulatory structure as the reticular formation of the brain stem, midbrain and thalamus.

Effects Upon the Reticular Structure

In a series of brilliant discoveries mainly in the past decade, it has been shown that the great central regulatory and integrating system is a core of gray matter extending from the medulla to the third ventricle, with forward projections through the mid-portion of the thalamus to the septum and on to the cortex as the nonspecific thalamocortical system (78, 79). According to current thought in physiology, the cerebral cortex is not a dominant but a highly specialized portion of the brain, which is capable of carrying on the many special functions characteristic of intellectual activity. It must, however, be roused to this activity by more primitive portions of the brain comprising the reticular structure and the nonspecific thalamocortical system. Incoming sensory stimuli pass not only via the specific sensory tracts through the thalamus to the sensory cortex; they pass also via connecting branches from the sensory tracts to the reticular activating system. This reticular activating system may be thought of as a master switchboard from which alerting signals are sent to the appropriate areas of the cortex, so that the incoming stimuli evoke the appropriate responses, including recognition, association and the initiation of motor and other responses. Moreover, other connections from this reticular system pass to the nuclei in the hypothalamus, subthalamus and brain stem which initiate the vascular and endocrine changes characteristic of the emotional responses to the incoming stimuli. In the absence of this activation of the cortex by the reticular structure, incoming stimuli have little or no effect. The cortex subsides into a state of sleep or repose and autonomic functions show a

preponderance of vagal effect characteristically associated with sleep. The reticular formation does not serve only to alert the cortex and hypothalamus. It is, rather, a selective regulator of both higher and lower levels of the nervous system, exerting both stimulatory and inhibitory influences (80) so that specific integrated patterns of response occur.

The interrelationships of these structures have been largely explored by the use of semimicro electrode techniques, by means of which simultaneous recordings of electrical activity are obtained from the various portions of the brain at rest, as modified by drugs, and as stimulated by incoming sensory stimuli. Using such methods, Horsey and Akert (81) and Caspers (77) have shown that alcohol exerts its first depressant action not upon the cerebral cortex itself but upon the reticular activating system. The degree of this depression is directly proportional to the amount of alcohol administered and, therefore, to the blood alcohol level reached. At first, mild depression of the reticular activating system results in a release of the cerebral cortex from selective control and inhibition. The effect is to eliminate the organized patterns of cortical electrical activity characteristic of the fully conscious waking state, and also to increase the excitability of the cortical cells, though not in a physiologically useful sense. In this state the cortex assumes a synchronous slow-wave pattern of electrical activity (77, 81, 82) and can easily be excited to electrical seizure at a much lower threshold than in the normal waking state. This effect of alcohol may well provide the basic explanation of the complex phenomena of alcohol intoxication. With loss of this integrating control the various portions of the nervous system are left, so to speak, to their own devices. Freed of central inhibition, the spinal reflexes may at first be increased, until much higher alcohol levels producing profound intoxication lead to local impairment of nervous function. Freed of central inhibition, gravitational stimuli on the vestibular apparatus evoke reflex positional nystagmus. Freed of selective control, cortical processes related to thought occur in a jumbled, disorganized fashion so that the thought content, the emotional tone and the form of expression show progressive loss of relevance to the surrounding situation. With the absence of the alerting function of the reticular system, incoming sensory stimuli and warning signals fail to make appropriate impact upon the cortex, so that the over-all reaction time involving recognition, association and ap-

propriate response is increased and sensory acuity is decreased. Finally, with the diminution of alertness, stimuli to the autonomic regulatory centers in the hypothalamus are modified to a pattern more nearly approximating that of sleep or rest. In very recent work, Goldberg and his associates have found that in the interval between the first and second phases of positional alcohol nystagmus, slow rhythmic rolling movements of the eyes occur which are identical with those seen during drowsiness induced by heat and humidity (63).

Most of the autonomic manifestations of alcohol intoxication can also be explained on the basis of a primary action on the reticular formation. The pleasant feeling of warmth induced even by low doses of alcohol, the well-known flushing of the skin, are not the result of a peripheral action of alcohol on the blood vessels but of a central action of alcohol on the vasomotor and thermoregulatory centers (83). Cutaneous flushing and increased sweating, which are typical of alcohol intoxication (84), as well as increased gastric acid secretion and increased peristalsis, which are produced by ethanol, are also typical of normal sleep and can be produced by experimental lesions in the reticular formation around the aqueduct of Sylvius where it enters the third ventricle (85–88).

Endocrine Effects

Certain endocrine effects of acute alcohol intoxication appear also to result from the action of alcohol upon the reticular formation and the hypothalamus. Many subjects, for example, show a diuresis of varying intensity and duration upon consuming alcohol. This diuresis is not explainable on the basis of any direct local action of alcohol upon the kidney. Rather, it is due to inhibition by alcohol of the release of antidiuretic hormone (ADH) from the posterior pituitary where it is stored, or from the supraoptic nucleus of the hypothalamus where it is formed (89–95). Pain, fear, nausea and other unpleasant sensations cause a release of ADH by stimulating the supraoptic nucleus via its nervous connections from the central reticular formation. Alcohol blocks the reticular structure and inhibits release of ADH. This is one apparent difference between alcohol intoxication and sleep, because normal sleep is characterized by ADH secretion, resulting in reduced urine volume and higher specific gravity. It may be, however, that ADH release during sleep is due to osmotic rather than to neurogenic stimuli.

There are many resemblances between ADH and the recently discovered factor from the hypothalamus which causes release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland; they are formed in closely related parts of the anterior hypothalamus, they appear to be similar chemically and their secretion is stimulated by the same types of physical and emotional stress (85–88). One might expect, then, that if alcohol suppresses the release of ADH, it would also suppress the secretion of the ACTH-releasing factor. Yet it has been claimed repeatedly (96–99) that alcohol stimulates the output of adrenocortical hormones by producing a release of ACTH from the hypophysis. In this sense, it has been considered that alcohol produces a nonspecific stress reaction which, if repeated too frequently, results in eventual exhaustion of the adrenal cortex and a state resembling Addison's disease. This has been used as the rationale for the treatment of alcoholism with ACTH or adrenocortical hormones (100). It is difficult to understand this concept in terms of spontaneous human drinking behavior. People do not drink alcohol in order to produce a state of stress but often to prevent or relieve one. If people drink alcohol to produce a relaxed and pleasant state, it seems more reasonable to expect that alcohol should decrease ACTH output. Forsander and his colleagues in fact reported that moderate doses of alcohol did not increase adrenal cortex output (101). In our own work we have found that moderate doses of alcohol given by stomach tube to rats tended, if anything, to diminish adrenal cortex activity as measured by acute changes in cholesterol and ascorbic acid level (102). The same dose of alcohol when given by intraperitoneal injection, resulting in an extremely rapid and higher rise in blood alcohol level, did indeed produce adrenal cortex stimulation, as might be expected from the sudden and profound respiratory and circulatory disturbances produced by the alcohol when given in this manner. This is an example of the type of situation in which sudden profound intoxication may produce results which are qualitatively quite different from those following intoxication achieved in the more usual manner by a slow rise in blood alcohol level.

One endocrine effect of alcohol intoxication which is not readily explained on the basis of a depression of the reticular formation is the disturbance in metabolism of adrenalin and noradrenalin. It has been shown by many investigators that even moderate doses of alcohol produce a prompt and significant increase in the urinary

excretion of adrenalin and noradrenalin (103–107), which has been interpreted by some as an indication that alcohol stimulates secretion of those hormones by the adrenal medulla, although there are recent reports which are not in agreement (108, 109). While most of the autonomic responses to alcohol intoxication, as we have seen, indicate vagal predominance, there are some changes suggesting sympathetic activity. For example, during the early stages of intoxication there is often some rise in blood pressure and pulse rate. The pupil is characteristically dilated rather than constricted. The blood sugar level at first rises, suggesting an adrenalin-like effect (103, 104, 110, 111), though it later falls to subnormal or even fatal levels (112) which may indicate a vagally induced hyperinsulinism. It is not clear, however, whether these signs of adrenalin effect and increased urinary catecholamine excretion really indicate an increased secretion or, rather, a displacement of catecholamines from their normal storage sites in the nervous system and adrenal medulla. Several findings favor the latter view. A single moderate dose of alcohol has been found to displace almost half of the adrenalin and noradrenalin from their normal sites in the brain stem (113), in a pattern similar to that produced by reserpine. The adrenalinlike effects of alcohol, therefore, may possibly not represent a true sympathetic stimulation but, quite the contrary, a temporary effect due to displacement of catecholamines analogous to the action of reserpine. This speculation remains to be proven. Another point to remember is that in human beings it is difficult to separate the effects of alcohol itself from the emotional effects of taking the forbidden fruit; it is noteworthy that alcohol given intravenously to a patient unaware of its identity produces only sedation and tranquility, without preliminary excitement.

Clinical Significance of Alcohol Action

Having explored at some length the actions of alcohol on the nervous system, we are naturally curious to examine their clinical significance. The first and most obvious question is: do these facts and conjectures shed any light on the question of why people drink and why some drink too much? We may reply that alcohol acts as a tranquilizer, to relieve tensions. This is too easy an answer, however, and not necessarily correct. Animal experiments (114–118) have given contradictory results with respect to the ability

of alcohol to decrease anxiety, but this may well be due to an inadequate definition of what constitutes anxiety, especially in a rat. Moreover, alcohol and drinking undoubtedly have many individual and social connotations that may not necessarily be related to the pharmacological actions of alcohol. There is no doubt, though, that alcohol does have a tranquilizer-like effect, and that it strongly potentiates the action of meprobamate (116, 119, 120). While this action of alcohol may not be a sufficient explanation of why a person begins to drink on any given occasion, it may well explain why he sometimes continues a drinking bout in apparently compulsive fashion.

Thus, it has been found that after a period of some hours, when the effect of alcohol has worn off, there may be not merely a return of the suppressed neurological functions but actually an overshooting. For example, alcohol in sufficient dose causes a rise in the threshold stimulus required to produce electroshock convulsions (121, 122). When the effect of alcohol wears off, the threshold for electroshock convulsions falls not merely to normal but to subnormal values (122) for several hours. After a prolonged period of alcohol intake, this period of lowered threshold to electroshock lasts for several days. Similarly, when the acute effects of alcohol intoxication wear off, the positional nystagmus, which appears early in the course of intoxication, first disappears and then reappears but with the nystagmus in the opposite direction (58–63). This occurs at a time which coincides with the decreased convulsion threshold noted in rats and with the subjective symptoms of hangover in man. It seems quite plausible, therefore, that withdrawal symptoms represent a rebound hyperactivity of those structures which alcohol suppresses, and that the compulsion of the alcoholic to keep drinking may be, at least in part, a protective device against these unpleasant symptoms, since even one drink can quickly reverse them (60).

The clinical treatment of alcohol intoxication and withdrawal symptoms has made heavy use of various phenothiazine and other tranquillizers. Their clinical effectiveness is undeniable, but it may be well to recognize that in their pharmacological actions they are very similar to the extra drink which the patient might otherwise take. They are effective because to a considerable extent they suppress the same structures that alcohol does. Goldberg (63) has recently demonstrated this equivalence of effect of alcohol and of

various phenothiazine antihistaminics in abolishing the second phase of positional alcohol nystagmus (the hangover phase). It is clear, therefore, that the risk of transfer of addiction from alcohol to tranquilizer should be kept in mind.

There are subjects, such as the effects of ethanol on body water and electrolyte distribution, coproporphyrin metabolism and exocrine secretion, which it has been impossible to cover in the space of this review. About many of these subjects there is only fragmentary knowledge and their significance is not yet clear. The material reviewed, however, may serve as a basis for the discussion of some of the clinical problems of alcoholism and its treatment.

Summary

The literature dealing with acute effects of moderate doses of alcohol on living cells, the liver and the nervous system (bibliography of 122 items) is reviewed and discussed, and the following conclusions are offered:

The degree of intoxication produced in the living organism depends not only on the concentration of alcohol but also on the rate at which it is reached. A subject may be more intoxicated at a given blood alcohol concentration if it is reached rapidly rather than slowly, and at the rise of the alcohol curve than at its decline. It is doubtful that concentrations of alcohol compatible with life ever affect directly any tissues but those of the nervous system and possibly of the liver.

The evidence concerning acute effects of alcohol upon a previously healthy liver is inadequate to permit any conclusion about possible effects other than nutritional ones.

Studies of simple reflexes and peripheral neurones suggest, but by no means demonstrate conclusively, that in moderately intoxicating concentrations alcohol acts primarily upon central mechanisms which affect the reflexes secondarily.

Neither biochemical nor neurophysiological evidence supports the idea that alcohol acts primarily and directly to depress the cerebral cortex. It seems likely that alcohol acts first upon some regulatory structure, probably the reticular formation of the brain stem, midbrain and thalamus, which modifies the activity of the cerebral cortex as well as that of the peripheral neurones and the

spinal and brain-stem reflexes. Alcohol intoxication may reflect the elimination of organized patterns of cortical electrical activity and increased excitability of cortical cells resulting from the first mild depression of the reticular activating system, with release of the cerebral cortex from selective control and inhibition. Most autonomic manifestations of alcohol intoxication and certain endocrine effects can also be explained on the basis of a primary action on the reticular formation.

REFERENCES

1. Harger, R. N. and Hulpieu, H. R. The pharmacology of alcohol. In: Thompson, G. N., ed. Alcoholism; ch. 2. Springfield, Ill.; Thomas; 1956.
2. Himwich, H. E. Alcohol and brain physiology. In: Thompson, G. N., ed. Alcoholism; ch. 4. Springfield, Ill.; Thomas; 1956.
3. Westerfeld, W. W. The metabolism of alcohol. Tex. Rep. Biol. Med. 13: 559–577, 1955.
4. Schulman, M. P., Zurek, R. and Westerfeld, W. W. The pathway of alcohol metabolism. In: Himwich, H. E., ed. Alcoholism; pp. 29–37. Washington, D.C.; American Association for the Advancement of Science; 1957.
5. Westerfeld, W. W. and Schulman, M. P. Some biochemical aspects of the alcohol problem. Quart. J. Stud. Alc. 20: 439–451, 1959.
6. Smith, M. E. and Newman, H. W. Ethanol-1-C^{14} and acetate-1-C^{14} incorporation into lipid fractions in the mouse. Proc. Soc. exp. Biol., N.Y. 104: 282–284, 1960.
7. Casier, H. and Polet, H. The metabolism of ethyl alcohol and acetaldehyde labeled with C^{14}. Arch. int. Pharmacodyn. 120: 498–501, 1959.
8. Forsander, O. A. and Räihä, N. C. R. Metabolites produced in the liver during alcohol intoxication. J. biol. Chem. 235: 34–36, 1960.
9. Schiller, D., Burbridge, T. N., Sutherland, V. C. and Simon, A. The conversion of labeled ethanol to glycerol and glycogen. Quart. J. Stud. Alc. 20: 432–438, 1959.
10. Koppanyi, T., Canary, J. J. and Maengwyn-Davies, G. D. Problems in acute alcohol poisoning. Quart. J. Stud. Alc., Suppl. No. 1, pp. 24–36, 1961.
11. Goldberg, L. Quantitative studies on alcohol tolerance in man. The influence of ethyl alcohol on sensory, motor and psychological functions referred to blood alcohol in normal and habituated individuals. Acta physiol. scand. 5 (Suppl. 16): 1–128, 1943.
12. Rosenbaum, M. Adaptation of the central nervous system to varying concentrations of alcohol in the blood. Arch. Neurol. Psychiat. 48: 1010–1012, 1942.
13. Mirsky, I. A., Piker, P., Rosenbaum, M. and Lederer, H. "Adaptation" of the central nervous system to varying concentrations of alcohol in the blood. Quart. J. Stud. Alc. 2: 35–45, 1941.
14. Best, C. H., Hartroft, W. S., Lucas, C. C. and Ridout, J. H. Liver damage produced by feeding alcohol or sugar and its prevention by choline. Brit. med. J. 2: 1001–1006, 1949.
15. Edmondson, H. A., Hall, E. M. and Myers, R. O. Pathology of alcoholism. In: Thompson, G. N., ed. Alcoholism; ch. 3. Springfield, Ill.; Thomas; 1956.

16. KLATSKIN, G. Effect of alcohol on the liver. J. Amer. med. Ass. 170: 1671–1676, 1959.
17. DAVIDSON, C. S. and POPPER, H. Cirrhosis in alcoholics. Amer. J. Med. 27: 193–195, 1959.
18. SHORTER, R. G. and BAGENSTOSS, A. H. Observations on the histogenesis of cirrhosis of the liver in chronic alcoholism. Amer. J. clin. Path. 32: 422–429, 1959.
19. POPPER, H., RUBIN, E., KRUS, S. and SCHAFFNER, F. Postnecrotic cirrhosis in alcoholics. Gastroenterology 39: 669–689, 1960.
20. MALLOV, S. and BLOCH, J. L. Role of hypophysis and adrenals in fatty infiltration of liver resulting from acute ethanol intoxication. Amer. J. Physiol. 184: 29–34, 1956.
21. DI LUZIO, N. R. Effect of acute ethanol intoxication on liver and plasma lipid fractions of the rat. Amer. J. Physiol. 194: 453–456, 1958.
22. HORNING, M. G., WILLIAMS, E. A., MALING, H. M., BRODIE, B. B. and BUTLER, W. M., JR. Depot fat as source of increased liver triglycerides after ethanol. Biochem. biophys. Res. Communic. 3: 635–640, 1960.
23. MALING, H. M., HORNING, M. G., BUTLER, W. M., JR., HIGHMAN, B. and BRODIE, B. B. Triglyceride deposition in rat liver through derangement of fat transport by various chemical agents. Fed. Proc. 19: 229, 1960.
24. BANG, N. U., IVERSEN, K., JAGT, T. and MADSEN, S. Serum glutamic oxalacetic transaminase activity in acute and chronic alcoholism. J. Amer. med. Ass. 168: 156–160, 1958.
25. MADSEN, S., BANG, N., IVERSEN, K. and JAGT, T. The influence of the diet on the serum glutamic oxaloacetic transaminase in acute intoxication of chronic alcoholics. Dan. med. Bull. 6: 33–37, 1959.
26. BAUER, R. and WOZASEK, O. Alcohol and liver function. Rev. Gastroenterol. 1: 95–103, 1934.
27. STENSTAM, T. Peroral and intravenous galactose tests. A comparative study of their significance in different conditions. Acta med. scand. Vol. 126, Suppl. 177, 115 pp. 1946.
28. GREENMAN, L., TIPPING, J. S. and ROSENBAUM, J. D. The influence of alcohol on the intravenous galactose tolerance test. Amer. J. med. Sci. 217: 644–650, 1949.
29. SERIANNI, E., LOLLI, G. and VENTURINI, M. The effects of solid food and of alcoholic beverages, especially wine, on the excretion of hippuric acid. Quart. J. Stud. Alc. 16: 67–85, 1955.
30. JELLINEK, E. M. and MCFARLAND, R. A. Analysis of psychological experiments on the effects of alcohol. Quart. J. Stud. Alc. 1: 272–371, 1940.
31. DREW, G. C., COLQUHOUN, W. P. and LONG, H. A. Effect of small doses of alcohol on a skill resembling driving. Brit. med. J. 2: 993–999, 1958.
32. GALLEGO, A. On the effect of ethyl alcohol upon frog nerve. J. cell. comp. Physiol. 31: 97–106, 1948.
33. KLENSCH, H. Über den Einfluss von Temperatur und Narkose auf die Erregbarkeit und Erregungsleitung des Kaltblüternerven. Pflüg. Arch. ges. Physiol. 251: 513–535, 1949.
34. LAPIQUE, L. and KAJIWARA, S. Changements dans les chronaxies périphériques sous l'influence de l'alcool. C.R. Soc. Biol. 105: 632–634, 1930.
35. COURTOIS, A. and NEOUSSIKINE, B. L'influence de l'alcool sur la chronaxie des muscles antagonistes chez l'homme, C.R. Soc. Biol. 113: 1342–1344, 1933.
36. MALAMUD, W., LINDEMANN, E. and JASPER, H. H. Effects of alcohol on the chronaxia of the motor system. Arch. Neurol. Psychiat. 29: 790–807, 1933.

37. Andreev, B. V. and Mayorov, F. P. Izmeneniya motornoi khronaksii u cheloveka pri alkogol'nom narkoze. (Changes in motor chronaxy in man during alcohol narcosis.) Fiziol. Zh. SSSR. **29**: 151–157, 1940.
38. Chauchard, P., Mazoué, H. and Lecoq, R. Recherches chronaximétriques sur l'intoxication alcoolique chronique expérimentale, essai de protection par les sucres et la vitamine B_1. C.R. Soc. Biol. **140**: 47–48, 1946.
39. Chauchard, P., Mazoué, H. and Lecoq, R. Les médications accélératrices et inhibitrices de l'intoxication alcoolique. C.R. Soc. Biol. **143**: 1550–1553, 1949.
40. Lecoq, R., Chauchard, P. and Mazoué, H. Suppression des troubles neuro-musculaires de l'alcoolisme chronique expérimental par injection ou ingestion de vitamines B_3 et B_4. C.R. Acad. Sci. **222**: 414–418, 1946.
41. Lecoq, R., Chauchard, P. and Mazoué, H. Contribution à l'étude du mode d'action du disulfure de tétraéthylthiuram et de l'apomorphine dans le traitement de l'alcoolisme chronique. C.R. Acad. Sci. **229**: 1261–1263, 1949.
42. Martin, R. and Le Breton, R. Etude de l'excitabilité neuro-musculaire sous l'influence de l'alcool. Ann. Méd. lég. **36**: 235–242, 1956.
43. Travis, L. E. and Dorsay, J. M. Effect of alcohol on the patellar tendon reflex time. Arch. Neurol. Psychiat. **21**: 613–624, 1929.
44. Tuttle, W. W. The effect of alcohol on the patellar tendon reflex. J. Pharmacol. **23**: 163–172, 1924.
45. Ikemune, I. Der Einfluss des verminderten Atmosphärendruckes auf die Reflexzeit. J. Okayama med. Soc. **52**: 1270–1275, 1940.
46. Kolmodin, G. M. The action of ethyl alcohol on the monosynaptic extensor reflex and the multisynaptic reflex. Acta physiol. scand. **29** (Suppl. 106): 530–537, 1953.
47. Johnson, E. W. and Olsen, K. J. Clinical value of motor nerve conduction velocity determination. J. Amer. med. Ass. **172**: 2030–2035, 1960.
48. Yanagihara, N., Inasaka, K. and Takenaka, K. [Effect of alcohol on the pinna reflex to sound.] (Japanese text.) Oto-rhino & laryng. Clin. **31**: 947–954, 1936. Abstract in Psychol. Absts **11**: 518–519, 1937.
49. Schwab, W. and Ey, W. Das hör und Gleichgewichtsorgan beim menschen unter akuter Alkoholeinwirkung. Münch. med. Wsch. **97**: 658–662, 1955.
50. Niemirowicz-Szczytt, C. Les modifications de la chronaxie vestibulaire déterminées par l'alcool chez les alcooliques. Encéphale **33**^{2}: 26–45, 1938.
51. Brun, M. Les modifications de la chronaxie vestibulaire chez les lapins sous l'influence de l'alcool. Encéphale **33**^{2}: 46–60, 1938.
52. Mouriquand, G., Coisnard, J. and Edel, V. Recherches bioclniques sur le vin; vin et indice chronologique vestibulaire. Pr. méd. **54**: 725, 1946.
53. Mouriquand, G., Coisnard, J. and Edel, V. Vin ordinaire, vin sucré et indice chronologique vestibulaire. C.R. Soc. Biol. **140**: 877–879, 1946.
54. Mouriquand, G., Edel, V. and Chighizola, R. Alcool et indice chronologique vestibulaire. C.R. Soc. Biol. **141**: 86, 1946.
55. Mouriquand, G., Edel, V. and Chighizola, R. Alcool pur, alcool dilué et indice chonologique vestibulaire. C.R. Soc. Biol. **141**: 87–88, 1946.
56. Mouriquand, G., Edel, V. and Chighizola, R. Sur la durée du temps d'imprégnation alcoolique mésurée par l'indice chronologique vestibulaire. C.R. Soc. Biol. **143**: 282–283, 1948.
57. Frenzel, H. Alkohollagenystagmus beim Menschen. Arch. Ohr.-, Nas.-, u. KehlkHeilk. **146**: 220–222, 1939.
58. Plenkers, J. Über lagenystagmus während akuter Alkoholintoxikation beim Menschen. Arch. Ohr.-, Nas.-, u. KehlkHeilk. **152**: 197–206, 1943.

59. WALTER, H. W. Alkoholmissbrauch und Alkohollagenystagmus. Dtsch. Z. ges. gerichtl. Med. 43: 232–241, 1954.
60. ASCHAN, G., BERGSTEDT, M., GOLDBERG, L. and LAURELL, L. Positional nystagmus in man during and after alcohol intoxication. Quart. J. Stud. Alc. 17: 381–405, 1956.
61. ASCHAN, G. Different types of alcohol nystagmus. Acta otolaryng., Stockh. Suppl. 140: 69–78, 1958.
62. ASCHAN, G., BERGSTEDT, M. and GOLDBERG, L. The effect of some antihistaminic drugs on positional alcohol nystagmus. Acta otolaryng., Stockh. Suppl. 140: 79–90, 1958.
63. GOLDBERG, L. Alcohol, tranquilizers and hangover. Quart. J. Stud. Alc., Suppl. No. 1, pp. 37–56, 1961.
64. HIMWICH, H. E., SYKOWSKI, P. and FAZEKAS, J. F. The effects of alcohol and pentobarbital on metabolism of excised cerebral tissues of adult and infant rats. Amer. J. Physiol. 129: 382–383, 1940.
65. FUHRMAN, F. A. and FIELD, J. Inhibition of brain respiration by ethyl alcohol at varied temperature levels. Proc. Soc. exp. Biol., N.Y. 69: 331–332, 1948.
66. GHOSH, J. J. and QUASTEL, J. H. Narcotics and brain respiration. Nature 174: 28–31, 1954.
67. SUTHERLAND, V. C., HINE, C. H. and BURBRIDGE, T. N. The effect of ethanol on cerebral cortex metabolism in vitro. J. Pharmacol. 116: 469–479, 1956.
68. FISCHER, E. The counteraction of weak concentrations of azide on the depressing effect of alcohol on the oxygen consumption of brain slices. In: HIMWICH, H. E., ed. Alcoholism; pp. 19–27. Washington, D.C.; American Association for the Advancement of Science; 1957.
69. BEER, C. T. and QUASTEL, J. H. The effects of aliphatic alcohols on the respiration of rat brain cortex slices and rat brain mitochondria. Canad. J. Biochem. Physiol. 36: 543–556, 1958.
70. WALLGREN, H. and KULONEN, E. Effect of ethanol on respiration of rat-brain-cortex slices. Biochem. J. 75: 150–158, 1960.
71. HINE, C. H., SHICK, A. F., MARGOLIS, L., BURBRIDGE, T. N. and SIMON, A. Effects of alcohol in small doses and tetraethylthiuramdisulphide (Antabus) on the cerebral blood flow and cerebral metabolism. J. Pharmacol. 106: 253–260, 1952.
72. BATTEY, L. L., HEYMAN, A. and PATTERSON, J. L., JR. Effects of ethyl alcohol on cerebral blood flow and metabolism. J. Amer. med. Ass. 152: 6–10, 1953.
73. FAZEKAS, J. F., ALBERT, S. N. and ALMAN, R. W. Influence of chlorpromazine and alcohol on cerebral hemodynamics and metabolism. Amer. J. med. Sci. 230: 128–132, 1955.
74. SUTHERLAND, V. C., BURBRIDGE, T. N., ADAMS, J. E. and SIMON, A. Cerebral metabolism in problem drinkers under the influence of alcohol and chlorpromazine hydrochloride. J. appl. Physiol. 15: 189–196, 1960.
75. VARÉ, G., VARÉ, P., VERDIER, H. and VIDACOVITCH, M. L'influence de l'alcool sur la chronaxie des centres psycho-moteurs. C.R. Soc. Biol. 103: 1255–1256, 1930.
76. SCHAFFARZICK, R. W. Anticonvulsive action of isopropyl alcohol. Proc. Soc. exp. Biol., N.Y. 74: 211–215, 1950.
77. CASPERS, H. Die Beeinflussung der corticalen Krampferregbarkeit durch das aufsteigende Reticulärsystem des Hirnstammes. *II.* Narkoswirkungen. Z. ges. exp. Med. 129: 582–606, 1958.
78. FRENCH, J. D. The reticular formation. In: MAGOUN, H. W., ed. Handbook of

Physiology; section I, vol. II, ch. 52. Washington, D.C.; American Physiological Society; 1960.

79. Jaspers, H. H. Unspecific thalamocortical relations. In: Magoun, H. W., ed. Handbook of Physiology; section I, vol. II, ch. 53. Washington, D.C.; American Physiological Society; 1960.
80. Fuster, J. M. Excitation and inhibition of neuronal firing in visual cortex by reticular stimulation. Science 133: 2011–2012, 1961.
81. Horsey, W. J. and Akert, K. The influence of ethyl alcohol on the spontaneous electrical activity on the cerebral cortex and subcortical structures of the cat. Quart. J. Stud. Alc. 14: 363–377, 1953.
82. Caspers, H. and Abele, G. Hirnelektrische untersuchungen zur Frage der quantitativen Beziehungen zwischen Blutalkoholgehalt und Alkoholeffekt. Dtsch. Z. ges. gerichtl. Med. 45: 492–509, 1956.
83. Siems, L. L. and Rottenstein, H. S. The locus of the peripheral vasodilator action of ethyl alcohol, tetraethylammonium and prescoline. Amer. J. med. Sci. 220: 649–654, 1950.
84. Graf, K. and Ström, G. Effect of ethanol ingestion on arm blood flow in healthy young men at rest and during leg work. Acta pharmacol. 17: 115–120, 1960.
85. Patton, H. D. and Amassian, V. E. The pyramidal tract: its excitation and functions. In: Magoun, H. W., ed. Handbook of Physiology; section I, vol. II, ch. 34. Washington, D.C.; American Physiological Society; 1960.
86. Uvnäs, B. Central cardiovascular control. In: Magoun, H. W., ed. Handbook of Physiology; section I, vol. II, ch. 44. Washington, D.C.; American Physiological Society; 1960.
87. Eliasson, S. G. Central control of digestive function. In: Magoun, H. W., ed. Handbook of Physiology; section I, vol. II, ch. 45. Washington, D.C.; American Physiological Society; 1960.
88. Ström, G. Central nervous regulation of body temperature. In: Magoun, H. W., ed. Handbook of Physiology; section I, vol. II, ch. 46. Washington, D.C.; American Physiological Society; 1960.
89. Eggleton, M. G. The diuretic action of alcohol in man. J. Physiol. 101: 172–191, 1942.
90. Eggleton, M. G. The effect of nicotine on the diuresis induced by ethyl alcohol. J. Physiol. 108: 482–490, 1949.
91. Strauss, M. B., Rosenbaum, J. D. and Nelson, W. P., III. Alcohol and homeostasis: the uncompensated diuresis induced by whiskey. J. clin. Invest. 28: 813–814, 1949.
92. Strauss, M. B., Rosenbaum, J. D. and Nelson, W. P., III. The effect of alcohol on the renal excretion of water and electrolyte. J. clin. Invest. 29: 1053–1058, 1950.
93. Van Dyke, H. B. and Ames, R. G. Alcohol diuresis. Acta endocrinol. 7: 110–121, 1951.
94. Rubini, M. E., Kleeman, C. R. and Lamdin, E. Studies on alcohol diuresis. *I.* The effect of ethyl alcohol ingestion on water, electrolyte and acid–base metabolism. J. clin. Invest. 34: 439–447, 1955.
95. Kleeman, C. R., Rubini, M. E., Lamdin, E. and Epstein, F. H. Studies on alcohol diuresis. *II.* The evaluation of ethyl alcohol as an inhibitor of the neurohypophysis. J. clin. Invest. 34: 448–455, 1955.
96. Smith, J. J. The effect of alcohol on the adrenal ascorbic acid and cholesterol of the rat. J. clin. Endocrin. 11: 792, 1951.

97. FORBES, J. C. and DUNCAN, G. M. The effect of acute alcohol intoxication on the adrenal glands of rats and guinea pigs. Quart. J. Stud. Alc. **12**: 355–359, 1951.

98. SANTISTEBAN, G. A. Adrenocortical influences upon the reconstitution of lymphatic tissue following acute involution. Endocrinology **64**: 638–647, 1959.

99. SANTISTEBAN, G. A. The response of the thymolymphatic system to graded doses of ethyl alcohol and its relationship to adrenocortical activity. Quart. J. Stud. Alc. **22**: 1–13, 1961.

100. SMITH, J. J. A medical approach to problem drinking; preliminary report. Quart. J. Stud. Alc. **10**: 251–257, 1949.

101. KRUSIUS, F.-E., VARTIA, K. O. and FORSANDER, O. Experimentelle Studien über die biologische Wirkung von Alkohol. 2. Alkohol und Nebennierenrinden-Funktion. Ann. Med. exp. fenn. **36**: 424–434, 1958.

102. CZAJA, C. and KALANT, H. The effect of acute alcohol intoxication on adrenal ascorbic acid and cholesterol in the rat. Canad. J. Biochem. Physiol. **39**: 327–334, 1961.

103. KLINGMAN, G. I. and GOODALL, M. Urinary epinephrine and levarterenol excretion during acute sublethal alcohol intoxication in dogs. J. Pharmacol. **121**: 313–318, 1957.

104. KLINGMAN, G. I., HAAG, H. B. and BANE, R. Studies on severe alcohol intoxication. *II*. Mechanisms involved in the production of hyperglycemia, hypokalemia and hemoconcentration. Quart. J. Stud. Alc. **19**: 543–552, 1958.

105. ABELIN, I., HERREN, C. and BERLI, W. Über die erregende Wirkung des Alkohols auf den Adrenalin- und Noradrenalinhaushalt des menschlichen Organismus. Helv. med. Acta **25**: 591–600, 1958.

106. PERMAN, E. S. The effect of ethyl alcohol on the secretion from the adrenal medulla in man. Acta physiol. scand. **44**: 241–247, 1958.

107. PERMAN, E. S. The effect of ethyl alcohol on the secretion from the adrenal medulla of the cat. Acta physiol. scand. **48**: 323–328, 1960.

108. GARLIND, T., GOLDBERG, L., GRAF, K., PERMAN, E. S., STRANDELL, T. and STRÖM, G. Effect of ethanol on circulatory, metabolic, and neurohormonal function during muscular work in men. Acta pharmacol. **17**: 106–114, 1960.

109. GIACOBINI, E., IZIKOWITZ, S. and WEGMANN, A. The urinary excretion of noradrenaline and adrenaline during acute alcohol intoxication in alcoholic addicts. Experientia **16**: 467, 1960.

110. FORSANDER, O., VARTIA, K. O. and KRUSIUS, F.-E. Experimentelle Studien über die biologische Wirkung von Alkohol. *I*. Alkohol und Blutzucker. Ann. Med. exp. fenn. **36**: 412–419, 1958.

111. LANGE, K. Blutzucker- und Blutalkoholspiegel bei weissen Ratten nach Alkoholbelastung und toxischer Leberschädigung. *I*. Der Blutzuckerspiegel. Hoppe-Seyl. Z. **321**: 49, 1960.

112. CUMMINS, L. H. Hypoglycemia and convulsions in children following alcohol ingestion. J. Pediat. **58**: 23–26, 1961.

113. GURSEY, D. and OLSEN, R. E. Depression of serotonin and norepinephrine levels in brain stem of rabbit by ethanol. Proc. Soc. exp. Biol., N.Y. **104**: 280–281, 1960.

114. KORMAN, M. Alcohol and anxiety levels in the albino rat: *I*, Observationally defined anxiety; *II*, Experimentally defined anxiety. Tex. Rep. Biol. Med. **18**: 34–42, 1960.

115. SCARBOROUGH, B. B. Lasting effects of alcohol on the reduction of anxiety in rats. J. genet. Psychol. **91**: 173–179, 1957.

116. KOPMANN, E. and HUGHES, F. W. Potentiating effect of alcohol on tranquilizers and other central depressants. A.M.A. Arch. gen. Psychiat. 1: 7–11, 1959.
117. CASEY, A. The effects of stress on the consumption of alcohol and reserpine. Quart. J. Stud. Alc. 21: 208–216, 1960.
118. KORN, S. J. The relationship between individual differences in the responsivity of rats to stress and intake of alcohol. Quart. J. Stud. Alc. 21: 605–617, 1960.
119. ZIRKLE, G. A., MCATEE, O. B., KING, P. D. and VAN DYKE, R. Meprobamate and small amounts of alcohol; effects on human ability, coordination, and judgment. J. Amer. med. Ass. 173: 1823–1825, 1960.
120. ZIRKLE, G. A. MCATEE, O. B., KING, P. D. and VAN DYKE, R. Effects of chlorpromazine and alcohol on coordination and judgement. J. Amer. med. Ass. 171: 1496–1499, 1959.
121. ALLAN, F. D. and SWINYARD, C. A. Evaluation of tissue tolerance to ethyl alcohol by alterations in electroshock seizure-threshold in rats. Anat. Rec. 103: 419, 1949.
122. MCQUARRIE, D. G. and FINGL, E. Effects of single doses and chronic administration of ethanol on experimental seizures in mice. J. Pharmacol. 124: 264–271, 1958.

Problems in Acute Alcohol Poisoning[1]

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MANY PROBLEMS of acute alcohol poisoning are so closely interwoven with those of alcoholism itself that the two can be separated only for didactic purposes. Toxic manifestations or fatal poisoning due to ethyl alcohol are most often seen in alcoholics who either overestimate their tolerance or purposely take an extraordinary quantity of spirits with suicidal intent. The common types of acute alcohol poisoning, too, usually occur in alcoholics. There is ample evidence that these excessive drinkers develop a marked tolerance to the pharmacological effects of alcohol but there is no proof that they acquire tolerance to an LD_{50} or an LD_{99} of ethanol. Koppanyi has shown that this is also true of a number of other aliphatic central nervous system depressants.

It is high time that the term "acute alcohol poisoning" be redefined and reevaluated. Koppanyi (1, 2) has defined acute alcohol intoxication as either (*a*) inebriation or excitement—characterized by ataxia, slurred speech, peripheral vasodilatation and combativeness—or (*b*) anesthesia or coma—characterized by pallor, various degrees of loss of reflexes (including corneal and pupillary reflexes), muscular relaxation, hypothermia, shallow and abdominal respiration, and fall of blood pressure which occasionally extends to peripheral vascular collapse. For present purposes, this definition should be expanded to include certain other acute manifestations seen in alcoholics which may possibly be due to alcohol but are more likely caused by specific or more general nutritional deficiencies. These syndromes occur suddenly, must be diagnosed early and require energetic treatment. Wernicke's syndrome is an example. Acute manifestations such as this, which are frequently encountered in alcoholics, should be considered part and parcel of alcohol poisoning.

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On the other hand, slowly developing diseases observed in alcoholics (e.g., portal cirrhosis or pancreatitis) and abstinence syndromes (e.g., delirium tremens, hallucinosis, alcoholic epilepsy) should not be considered acute alcoholic syndromes. A great deal of research is needed to determine the etiology of these diseases apart from alcoholism. Possible genetic predisposition or induction of adaptive enzymes (3)—in short, biochemical mechanisms—should be systematically investigated.

One further complication of alcohol toxicity is the so-called "acetaldehyde syndrome." This consists of various symptoms ranging from vasodilatation and vomiting to unconsciousness and cardiovascular collapse and occurs in individuals who take alcohol during or shortly after medication with a drug such as disulfiram or cyanamide (4). These agents produce a disturbance of alcohol metabolism leading to a considerable accumulation of acetaldehyde, which is most probably the metabolite that combines with alcohol to cause the symptoms. An additional explanation for this syndrome has been proposed by Christensen (5), Nelson (6) and Koppanyi (7), who have pointed out that acetaldehyde is, in fact, a sympathetic stimulant possessing both vasoconstrictor and vasodilator effects.

Acute Alcohol Intoxication

According to Victor and Adams (8), 20 per cent of the total number of alcoholics admitted to hospitals are severely intoxicated. These authors emphasize, however, that for each one who is actually admitted, approximately 10 are encountered in the emergency ward only and discharged without hospitalization. The blood alcohol levels in acutely inebriated patients range from 10 to 300 mg. per 100 ml. Their symptoms vary from euphoria to actual stupor. In the stuporous state the patient is capable neither of communicating nor of understanding spoken words. He sleeps with heavy breathing but when awakened fights violently the attendants who attempt to take care of him.

The effect of alcohol on the central nervous system is purely depressant. Even the mildest form of inebriation, when the patient appears stimulated, is due to a release phenomenon—probably mediated by a depression of cortical inhibition via the reticular activating system and other neural regions. As inebriation becomes more severe, motor and sensory depression becomes increasingly apparent.

The only important exception to this depressant effect on the central nervous system is the stimulation of the central vomiting mechanism. This is undoubtedly due partly to reflexes from the upper gastrointestinal tract or from the labyrinth and partly to direct stimulation either by ethanol itself or by one of its metabolites, possibly acetaldehyde.

A great variety of therapeutic procedures have been suggested for the intoxicated alcoholic. It is a routine measure to treat the troublesome patient either with hypnotics, such as paraldehyde or barbiturates, or, more recently, with tranquilizers such as the phenothiazines or chlordiazepoxide.[2] There is a certain risk involved in the use of sedation in patients whose blood alcohol concentration exceeds 150 mg. per 100 ml. These agents may act as additive synergistic central nervous system depressants or may even potentiate the depressant effects of alcohol, so that the patient may become comatose. The greatest care must be exercised during such treatment to prevent this. McDonald and Koppanyi[3] have repeatedly seen a rapid conversion of inebriation to coma, and Koppanyi (2) saw one case of a violent alcoholic who was given, slowly by vein, 0.3 g. of sodium amobarbital, resulting in immediate cessation of respiration followed by death, despite resuscitation measures. Further evidence of this danger can be seen in a study of the effects of intraperitoneal injection of ethanol and chlorpromazine on mice weighing 20 g. each, which produced the following results: Of 17 mice each injected with 0.05 ml. of 95-per-cent ethanol, none slept. Of 15 mice given 5.0 mg. of chlorpromazine per kg. of body weight, none slept. Of 19 mice given ethanol and chlorpromazine simultaneously in the above dosages, 3 did not fall asleep, 13 slept for an average of 175 minutes and 3 died.

In 1957 Koppanyi (1, 2) reviewed the treatment of acute alcohol intoxication. Since that time there have been several developments in this field: (*a*) The inefficacy of intravenous fructose in this treatment has now been substantiated in our laboratory (9). (*b*) Since low serum magnesium concentration has often been found in patients with alcoholism (10–13), McCollister, Flink and Doe (14) have performed magnesium balance studies in alcoholics and have found a positive magnesium balance in patients treated with special diet or parenteral magnesium or both. Similar therapy

[2] Librium, Hoffmann–La Roche, Inc.
[3] Unpublished data.

should be tested in acute inebriation. (*c*) A report on the efficacy of *l*-triiodothyronine in inebriation has recently appeared in the literature (15). The acetic acid analog of this hormone, in view of the still more rapid onset of its action, might be more effective. The biochemical rationale of this type of treatment, as will be pointed out later, is still obscure.

Alcoholic Coma

Alcohol, like other aliphatic narcotics, may produce surgical anesthesia. Its oil–water partition coefficient is very small (less than 1.0). For full anesthesia, about 2.5 ml. of alcohol per kg. of body weight in a 5-per-cent dextrose solution may be administered intravenously, the LD_{50} being about 7 ml. per kg. Alcohol anesthesia, however, is a hazardous undertaking because, as yet, alcohol metabolism cannot be regulated with safety and even the usual anesthetic dose may cause death. The margin of safety is, therefore, too narrow for practical purposes.

Alcohol coma resembles intravenous alcohol anesthesia with the exception that in the former case the drug has been taken orally. Even upon oral administration, alcohol is absorbed very quickly, the rate depending to a large extent upon the gastric contents. Therefore, alcoholic coma should be treated as any overdosage by an anesthetic agent, particularly by a fixed, nonvolatile anesthetic or hypnotic.

The many treatments for alcoholic coma that have been proposed have been enumerated and evaluated by Koppanyi (1, 2). Existing analeptics have been found to be of little value and it now appears that the so-called Scandinavian method, originally proposed by Nilsson (16), is the most applicable. This method has been described by Clemmesen and Nilsson (17) and may be summarized as follows:

1. Since alcohol is so very quickly absorbed, gastric lavage is not only unnecessary but may even be dangerous because of the possible aspiration of the gastric contents.

2. Patency of the airway must be tested. Should the airway not be patent, clearance of the air passage by suction or other methods is essential. Should the patient show complete areflexia, a pharyngeal airway or an endotracheal tube must be inserted. If the patient does not respire, artificial ventilation must be instituted immediately.

The foregoing measures apply to all comatose states. Speed is of

the utmost importance; hematological and chemical studies should therefore not be started until the above urgent therapeutic measures have been accomplished.

3. The smell of alcohol on the patient's breath does not constitute proof of alcohol intoxication, since the patient may have taken (and often does take) other central nervous system depressant agents with an alcoholic beverage. Therefore, determination of the blood alcohol level is essential. Only if the level is between 300 and 900 mg. per 100 ml. can the coma be attributed to alcohol. This wide range of the seriously toxic concentrations of this drug is not astounding in view of individual variability in the response to drugs, particularly to agents affecting the central nervous system. Blood grouping and crossmatching should be included in the hematological studies in order to be adequately prepared for the possible necessity of blood transfusions.

4. Continued care should be taken that adequate uptake of oxygen and output of carbon dioxide is maintained. This should be ascertained by frequent observations by the same physician and by determinations of blood oxygen content and oxygen capacity. The patient should be turned in bed every 2 or 3 hours in order to avoid atelectasis and bronchopneumonia. Clemmesen and Nilsson also recommended prophylactic penicillin medication, in doses of 2 to 5 million units, twice daily. The usefulness of this antibiotic as a preventive measure in such cases, however, is by no means established. In fact, in cases of kerosene poisoning it has been shown that the mortality rate does not change with antibiotic medication.

5. If the blood pressure is low and a rapid feeble pulse is observed, blood transfusion and injection of concentrated plasma or plasma expander may be instituted.

6. The patient should be kept warm; his kidney function and electrolyte balance must be determined and remedial measures instituted if needed.

The intravenous infusion of large amounts of physiological salt solution has protected dogs from an LD_{99} of ethanol (Table 1). The excess fluid, with its alcohol content, is excreted in the form of urine. Comatose patients treated in this way should be catheterized and the infusions regulated in accordance with urine flow in order to forestall pulmonary and cerebral edema as well as possible cardiac embarrassment.

Since ethanol is freely miscible with water, it lends itself ideally to removal by hemodialysis. This method has been applied to both ethanol and methanol (18) and it was found that in dogs with an initial blood alcohol level of 520 mg. per 100 ml. hemodialysis for

TABLE 1.—*Effect of Massive Intravenous Infusions of 1-per-Cent Sodium Chloride in Dogs Poisoned Orally with Ethanol*

				Results*	
Weight (*kg.*)	Ethanol Dosage (*g./kg.*)	Sodium Chloride Infusion (*ml.*)	Infusion Time (*hr:min.*)	Time to Recovery (*hr:min.*)	Time to Death (*hr:min.*)
7.6	9.6	—	—		3:30
8.5	9.6	—	—		5:30
10.0	9.6	—	—		4:40
7.8	9.6	—	—	75:00	
6.5	9.6	—	—	62:00	
6.9	9.6	—	—		4:10
11.0	12.0	—	—		2:52
8.4	12.0	—	—		3:06
8.7	12.0	—	—		6:00
8.1	12.0	—	—		5:15
7.6	12.0	—	—		2:40
15.0	15.0	6,600	4:00	48:00	
9.1	15.0	3,000	3:30	41:00	
8.7	15.0	2,800	2:30	39:00	
8.1	15.0	2,700	3:00	37:00	
8.0	15.0	2,700	3:00	46:00	
7.8	17.0	2,700	3:30	40:00	
7.6	17.0	2,600	3:00	38:00	
6.0	17.0	2,100	2:00	28:30	
6.7	17.0	2,300	2:00	39:00	
15.1	20.0	2,700	2:30		3:00
10.9	20.0	3,000	3:30	52:00	
10.2	20.0	3,000	3:30		2:40
9.6	20.0	3,000	3:30	58:00	

* From 20 to 30 per cent of the volume of the total infusate was excreted in the urine during the infusion; from 40 to 90 per cent within 24 hr. after the beginning of the infusion.

3 hr. reduced this level to about 175, whereas the nondialyzed animal still showed approximately 240 mg. per 100 ml. after 10 hr. (Figure 1). These results indicate the importance of therapy, and particularly early therapy, with the artificial kidney in the treatment of ethanol poisoning.

The last two methods have been tried in fewer than 10 patients, but with very satisfactory results.[4] These two methods are not necessarily mutually exclusive. If hemodialysis were undertaken, using the usual electrolyte mixture in the bath plus an inert material

[4] SCHREINER, G. E. [Personal communication.]

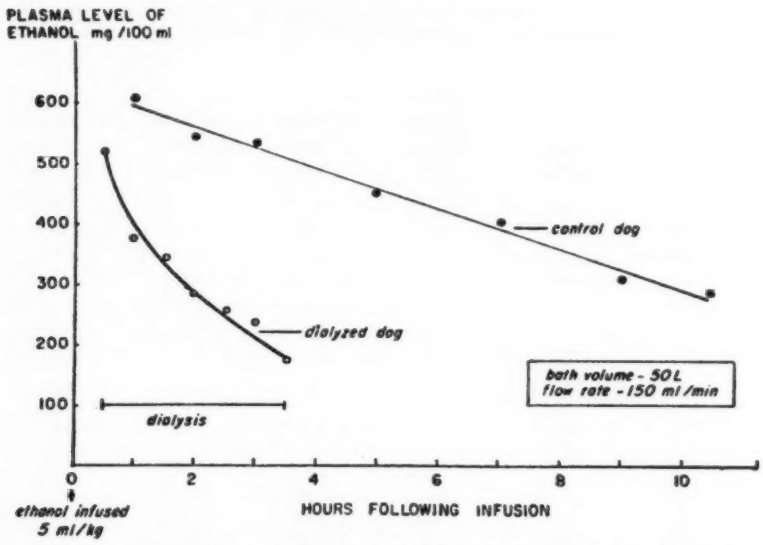

FIGURE 1.—*Comparison of Blood Alcohol Levels in Dialyzed and Control Dogs Following Infusion of 5 Ml. of Ethanol per Kg. of Body Weight.* From Marc-Aurele and Schreiner (18). Reproduced by permission from the *Journal of Clinical Investigation.*

to increase substantially the osmotic pressure of the bath fluid, then an intravenous infusion of large amounts of physiological salt solution would produce hemodilution and large amounts of water containing alcohol would escape into the bath fluid without the otherwise inherent danger of hemoconcentration.

Another possible means of accomplishing effective and immediate dilution of high blood alcohol levels is crosscirculation. Such a method has been used successfully in dogs for agents other than alcohol (19). The left carotid artery of the first animal was connected to the right external jugular vein of the second, and the right carotid artery of the second animal was connected to the left external jugular vein of the first. For barbital, which like alcohol is distributed with body water but which, in contrast to alcohol, is not metabolized at all for practical purposes, crosscirculation reduced the duration of anesthesia to 27 min. In comparison, non-crosscirculated animals slept for 29 hr. Thus this method reduced the sleeping time to approximately one-sixtieth of the control values.

Parenteral administration of magnesium salts, while recommended

in the treatment of inebriation, is contraindicated in alcoholic coma since magnesium is a powerful anesthetic and will synergize to a varying degree with the depressant effects of ethanol on the central nervous system.

Goldberg, Hehir and Hurowitz (15) employed l-tri-iodothyronine mainly for the treatment of noncomatose acutely intoxicated alcoholics whose blood levels ranged from 198 to 450 mg. per 100 ml.—the latter level approaching the lethal limits of alcohol intoxication (2, 20). This is apparently the first well substantiated report of a drug which causes objective and subjective effects by increasing the rate of alcohol disappearance (Figure 2). Of 20 intoxicated patients who were used for this study, 12 received 200 microg. of tri-iodothyronine intravenously and 8 remained untreated as controls. The initial blood alcohol levels in these two groups of patients were comparable. While the hourly rate of decline in blood alcohol in the control patients was 15±2.21 mg. per 100 ml., the group treated with tri-iodothyronine showed a mean hourly decline of 32.1±5.28 mg. per 100 ml. This difference in alcohol metabolism

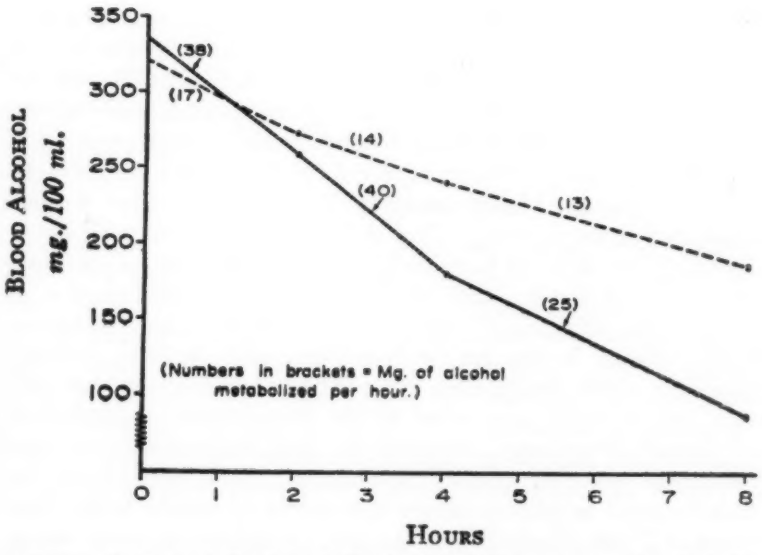

Figure 2.—*Rate of Decline of Blood Alcohol Concentration in Alcoholic Patients Treated with Tri-iodothyronine and in Alcoholic Controls.* Solid line: treated patients. Broken line: controls. From Goldberg, Hehir and Hurowitz (15). Reproduced by permission from the *New England Journal of Medicine.*

rate is highly significant. By doubling the rate of alcohol metabolism tri-iodothyronine produced sobering-up, or in the more severe cases awakening, in less than 2 hr., as judged by various clinical criteria.

The role of tri-iodothyronine as an activator of alcohol metabolism is probably not related to the acceleration of general tissue metabolism, in which this hormone shows a lag time of approximately 8 hr., although judged by relatively few parameters. Further study is needed to corroborate these findings and to determine the means by which this drug affects alcohol metabolism.

Other Acute Manifestations in Alcoholics

The clinical syndromes of Wernicke and Korsakoff may be classified under the general heading of nutritional disorders of nervous tissue. The clinical entities of these diseases will not be detailed here. Although these two syndromes are not directly produced by alcohol, they occur frequently in alcoholics. Pathological changes similar to those seen in Wernicke's encephalopathy have been shown in the brains of thiamin-deficient animals (21–24). In a recent symposium (25), several additional pertinent observations were reported. In Oriental beriberi, the Wernicke syndrome and the Korsakoff psychosis are not observed. This may be due in part to a more complete thiamin deprivation in alcoholics than in patients with beriberi and in part to stress superimposed on the vitamin deficient state of the alcoholic. Vomiting, for example, represents a particular stress in the wake of which Wernicke's disease may become apparent. Phillips and his coworkers (26) have further elucidated these problems. They studied patients with well documented Wernicke's and Korsakoff's syndromes who were maintained with a diet of glucose, minerals and water. With the exception of thiamin, the addition of isolated chemically pure representatives of the vitamin B complex produced no results in these patients. However, within hours after the addition of thiamin to this regimen, improvement was noted in the neurological manifestations of Wernicke's syndrome, although the Korsakoff amnesia and confabulation remained relatively unchanged. Victor and Adams (8) demonstrated in patients whose sole source of caloric intake consisted of 1 pint of whisky per day that alcohol per se could not be the etiological factor in Wernicke's syndrome. On this "diet," thiamin produced immediate improvement of the neurological disorder. At the clinical level, it appears that Wernicke's syndrome

is generally reversible while the Korsakoff syndrome, at least in some patients, appears permanent. Obviously a Korsakoff patient is not a normal individual and, upon readministration of a diet excessively high in carbohydrate and insufficiently covered by thiamin, Wernicke's syndrome again reappears. This observation immediately leads to the obvious conclusion that Wernicke's syndrome must be based on a reversible deficit. The exact nature of this biochemical disturbance has not yet been fully elucidated in spite of numerous investigations. The treatment of these acute manifestations is clearly defined: initial administration of thiamin parenterally and, upon recovery, a well-chosen diet rich in B-complex vitamins.

Other acute manifestations in alcoholics may be due to multiple nutritional deficiencies, possibly determined by the type of alcoholic beverage that is being consumed to excess. A degenerative disease of the corpus callosum (Marchiafava–Bignami syndrome) is limited to populations—usually but not exclusively of Italian stock—who consume large quantities of wine. There is no specific treatment for this condition.

Syndromes which are associated with the abrupt withdrawal of alcohol will not be discussed here. However, the possibility should be noted that the reason withdrawal from alcohol is sometimes not clearly delineated, particularly in a hospitalized patient, is that the administration of aldehydes and barbiturates may substitute for alcohol.

The "Acetaldehyde Syndrome"

The genesis of the acetaldehyde syndrome was discussed earlier. Treatment must be directed to the symptoms (e.g., vomiting or cardiovascular symptoms) as they arise. Oxygen administration and possibly intravenous injection of suitable iron preparations, with or without ascorbic acid, may be indicated in severe cases. Although Jokivartio (27) has reported that the entire acetaldehyde syndrome could be suppressed by the intravenous injection of ferrous chloride, other investigators have found that similar doses of iron preparations do not lower the acetaldehyde level (28).

Summary and Conclusions

Four types of acute alcohol poisoning are described: acute alcohol intoxication, alcoholic coma, Wernicke's and Korsakoff's syndromes and the "acetaldehyde syndrome" resulting from the con-

current ingestion of alcohol and drugs such as disulfiram or cyanamide. The last two were included because of the fulminating nature of these entities in alcoholics. Acute alcohol poisoning cannot be separated completely from alcoholism, since a considerable proportion of the former condition is observed in alcohol addicts. No drug therapy, with the possible exception of intravenous *l*-triiodothyronine administration, can produce a significant increase in alcohol metabolism. This includes glucose–insulin infusions as well as parenteral fructose or vitamin administration.

Intoxicated alcoholics may require sedation under strict and constant supervision so that the sedative or tranquilizing drugs will not aggravate the depression of the central nervous system which is often masked in the alcoholic excitement stage.

Symptomatic therapy, maintaining satisfactory ventilation and cardiovascular–renal function, is probably the safest and simplest measure in the management of alcoholic coma.

Increased elimination of alcohol by massive intravenous infusions of physiological salt solution, or by hemodialysis using the artificial kidney, have been eminently successful in the treatment of acute alcohol poisoning in dogs.

Thiamin is specific in Wernicke's syndrome, but Korsakoff's psychosis does not respond well to vitamin B_1 administration. In Korsakoff's psychosis large doses of intravenous glucose insufficiently covered with thiamin may precipitate Wernicke's encephalopathy.

The toxicity of even small amounts of alcohol in patients under the influence of disulfiram or cyanamide produces symptoms which should be treated as they develop; intravenous iron administration in these conditions may be helpful.

Alcoholism and its treatment, despite many important and useful contributions by medical science, is still basically an unsolved problem requiring continued and careful scrutiny by scientists, practitioners, and an enlightened society.

REFERENCES

1. KOPPANYI, T. Treatment of acute ethanol intoxication. J. forens. Med. 4: 132–141, 1957.
2. KOPPANYI, T. Treatment of acute alcoholic poisoning. In: HIMWICH, H. E., ed. Alcoholism: Basic Aspects and Treatment; pp. 93–113. Washington, D.C.; American Association for the Advancement of Science; 1957.

3. Aebi, von H. and von Wartburg, J. P. Vergleichhend-biologische Aspekte der experimentellen Enforschung chronischer Alkoholwirkungen. Bull. schweiz. Akad. med. Wiss. **16**: 25–35, 1960.
4. Warson, M. D. and Ferguson, J. K. W. Effects of cyanamide and ethanol on bleeding weight and blood acetaldehyde in mice and rats. Quart. J. Stud. Alc. **16**: 607–613, 1955.
5. Christensen, J. A. Mechanism of the action of tetraethylthiuram disulfide in alcoholism; iron as an antidote for the tetd–alcohol reaction. Quart. J. Stud. Alc. **12**: 30–39, 1951.
6. Nelson, E. E. Pressor response to acetaldehyde and its potentiation by cocaine. Proc. Soc. exp. Biol., N.Y. **52**: 23–24, 1943.
7. Koppanyi, T. Acetaldehyde, a volatile anesthetic and sympathetic stimulant. Anesthesiology **6**: 603–611, 1945.
8. Victor, M. and Adams, R. D. The effect of alcohol on the nervous system. Res. Publ. Ass. nerv. ment. Dis. **32**: 526–573, 1953.
9. Avery, M. A. Evaluation of fructose for alcohol poisoning. Bull. Georgetown Univ. med. Center **11**: 79–83, 1958.
10. Flink, E. B., Stutzman, F. L., Anderson, A. R., Konig, T. and Fraser, R. Magnesium deficiency after prolonged parenteral fluid administration and after chronic alcoholism complicated by delirium tremens. J. Lab. clin. Med. **43**: 169–183, 1954.
11. Flink, E. B. Magnesium deficiency syndrome in man. J. Amer. med. Ass. **160**: 1406–1409, 1956.
12. Flink, E. B., McCollister, R., Prasad, A. S., Melby, J. C. and Doe, R. P. Evidences for clinical magnesium deficiency. Ann. intern. Med. **47**: 956–968, 1957.
13. Martin, H. E., McCuskey, C., Jr. and Tupikova, N. Electrolyte disturbance in acute alcoholism, with particular reference to magnesium. Amer. J. clin. Nutrit. **7**: 191–196, 1959.
14. McCollister, R. J., Flink, E. B. and Doe, R. P. Magnesium balance studies in chronic alcoholism. J. Lab. clin. Med. **55**: 98–104, 1960.
15. Goldberg, M., Hehir, R. and Hurowitz, M. Intravenous tri-iodothyronine in acute alcoholic intoxication. New Engl. J. Med. **263**: 1336–1339, 1960.
16. Nilsson, E. On treatment of barbiturate poisoning; a modified clinical aspect. Acta med. scand. **139** (Suppl. 253): 1–127, 1951.
17. Clemmesen, C. and Nilsson, E. Therapeutic trends in the treatment of barbiturate poisoning. Clin. Pharmacol. Therap. **2**: 220–229, 1961.
18. Marc-Aurele, J. and Schreiner, G. E. The dialysance of ethanol and methanol: a proposed method for the treatment of massive intoxication by ethyl or methyl alcohol. J. clin. Invest. **39**: 802–807, 1960.
19. Koppanyi, T. and Linegar, C. R. Cross-circulation as a method in the study of drug fixation and poisoning. Science **96**: 562–563, 1942.
20. Kaye, S. and Haag, H. B. Terminal blood-alcohol concentrations in ninety-four fatal cases of acute alcoholism. J. Amer. med. Ass. **165**: 451–452, 1957.
21. Alexander, L., Pijoan, M. and Myerson, A. Beri-beri and scurvy; experimental study. Trans. Amer. neurol. Ass. **64**: 135–139, 1938.
22. Alexander, L. Wernicke's disease; identity of lesions produced experimentally by B_1 avitaminosis in pigeons with hemorrhagic polioencephalitis occurring in chronic alcoholism in man. Amer. J. Path. **16**: 61–70, 1940.
23. Prickett, C. O. Effect of deficiency of vitamin B_1 upon central and peripheral nervous system of rat. Amer. J. Physiol. **107**: 459–470, 1934.

24. RINEHART, J. F., FRIEDMAN, M. and GREENBERG, L. A. Effect of experimental thiamine deficiency on nervous system of rhesus monkey. Arch. Path. 48: 129–139, 1949.
25. KINNEY, T. D. and FOLLIS, R. H., JR., eds. Nutritional disease. Proceedings of a Conference on Beri-beri, Endemic Goiter and Hypovitaminosis A. Fed. Proc. 17 (Suppl. 2): 1–162, 1958.
26. PHILLIPS, G. B., VICTOR, M., ADAMS, R. D. and DAVIDSON, C. S. Study of nutritional defect in Wernicke's syndrome; effect of purified diet, thiamine, and other vitamins on clinical manifestations. J. clin. Invest. 31: 859–871, 1952.
27. JOKIVARTIO, E. Effect of iron preparations on "Antabuse"-alcohol toxicosis. Quart. J. Stud. Alc. 11: 183–189, 1950.
28. LESTER, D. and GREENBERG, L. A. Role of acetaldehyde in toxicity of tetraethylthiuram disulfide and alcohol. With method for determination of acetaldehyde in 0.20 ml. of blood. Quart. J. Stud. Alc. 11: 391–395, 1950.

Alcohol, Tranquilizers and Hangover[1]

Leonard Goldberg, M.D.[2]

OBSERVATIONS on nystagmus in connection with alcohol ingestion in man date back to the work of Joffroy and Serveaux (1) in 1897 and Bárány (2, 3) in 1911, and this phenomenon has been the subject of study subsequently by many workers (4–11). Methods of objectively and quantitatively measuring eye movements have opened new ways to study the action of alcohol on higher nerve centers.

Basic quantitative studies of various forms of alcohol-caused nystagmus in man were carried out by Aschan et al. (11) in 1956 using a device based on recording the standing potential of the eyes, with the eye bulbs acting as dipoles. These workers found that a single dose of alcohol induced two separate phases of positional alcohol nystagmus (PAN), mainly behind closed eyelids with the head in lateral positions. A first nystagmus phase (PAN I), was observed beginning ½ to 1 hour after alcohol ingestion and lasting for 3 to 4 hr. This was separated by an intermediate period of 1 to 2 hr. from a second phase (PAN II), with the nystagmus in the opposite direction from that of PAN I. Phase II began 5 to 6 hr. after ingestion and lasted for 5 to 10 hr., continuing in every single case for hours after alcohol had disappeared from the body. Thus phase II is an example of an objective aftereffect of alcohol.

Aschan (12) demonstrated an optokinetic alcohol gaze nystagmus (AGN), elicited by fixing the gaze in a lateral direction 30° to 40°. AGN in many respects differed from the two-phase PAN. Aschan, Bergstedt and Goldberg (13) showed that certain central nervous system depressant antihistamines reduce the intensity of PAN II, but increase AGN. Finally, these workers have studied the effects of prolonged intake of alcohol on the induced PAN[3] and the effect

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[3] ASCHAN, G., BERGSTEDT, M. and GOLDBERG, L. [To be published.]

of a new alcohol dose administered at the height of phase II, as an introduction to studies on hangover.

Systematic studies on the interaction between central nervous system depressant drugs—analgesics, antihistamines, sedatives and tranquilizers—and alcohol have been started in the Department of Alcohol Research at the Karolinska Institutet, using electrooculography (EOG) as one of many objective methods of recording changes in the central nervous system. These investigations have had two main objectives: to study the nature of the interplay between alcohol and other drugs affecting the central nervous system; and to elucidate the mechanisms and sites of action of the changes found.

Two main lines of approach have been followed. First, electroencephalographic (EEG) equipment was added to the recording instruments used and the relation between EEG and EOG findings, particularly on the effect of tranquilizers, was studied. These experiments were started in 1958 in cooperation with Doctor H. W. Newman[4] and have been continued at the Karolinska Institutet. Second, a quantitative study of the interaction between alcohol, tranquilizers and hangover has been started. Changes in coordination were assessed by measuring standing steadiness. Emphasis was placed on analyzing the occurrence and intensity in EOG records of roving ocular movements (ROM) and their interaction with existing PAN.

The aims of the present communication are as follows:

1. To present a picture, based on EOG records, of the effects and aftereffects of alcohol, particularly PAN and ROM.

2. To discuss the nature of the hangover syndrome and to demonstrate through EOG recordings some effects of alcohol in that stage.

3. To emphasize differences in effects and aftereffects of various alcoholic beverages in relation to differences in blood alcohol levels.

4. To analyze the occurrence and intensity of ROM, under normal conditions, during and after alcohol intake, and during hangover.

5. To show the relation of ROM to heat and humidity.

6. To present a picture of the interaction between alcohol and tranquilizing drugs based on changes in PAN and ROM.

7. To draw inferences from the findings presented as to the nature of alcoholism with special reference to the symptoms of withdrawal from alcohol and of desire or craving for alcohol during abstinence.

Some of the data concerning PAN connected with Point *1* above have been published (11). Observations concerning Point *2* have

[4] Division of Neurology, Stanford University. (Deceased, 19 September 1959.)

been presented in part before the Swedish Medical Society (14). Some preliminary results related to Points 3–7 were presented at the 26th International Congress on Alcohol and Alcoholism in Stockholm in August 1960 (15).

Methods

Subjects

The experiments were performed on 80 healthy subjects, 20 to 46 years of age, weighing 61 to 89 kg. All were accustomed to moderate alcohol consumption. The results reported in this communication are based on a total of 224 experiments.

Electrooculography (EOG)

This method is based on recording the standing electrical potential between the cornea and the retina of the eyes. The recording electrodes were placed at the outer corners of the eyes for horizontal recording, the eye bulbs acting as dipoles (Figure 1).

The potentials picked up were amplified in an A.C. preamplifier and

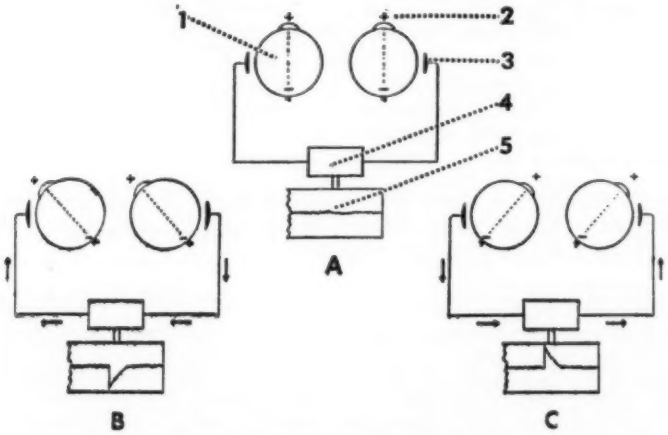

Figure 1.—*Principles of EOG (Electrooculographic) Recording.* *1* = Eye bulbs. *2* = Standing potential between cornea (+) and retina (−). *3* = Recording electrodes for horizontal recording on outer corners of eyes (grounding electrode on forehead not shown). *4* = Recording device (preamplifier, amplifier and ink recorder). *5* = Recorded curve of ocular movements. *A* = Eyes looking straight forward: No current is elicited through recorder; only small irregular deflections are seen on curve. *B* = Eyes looking to the left: Current is elicited through recorder; curve shows downward (left) deflection. *C* = Eyes looking to the right: Current is elicited through recorder; curve shows upward (right) deflection.

amplifier with long time constants (1.7 to 2.3 seconds) and recorded by means of an ink-writer via a specially built galvanometer equipped with a small glass bulb ending with a nozzle, 0.01 mm. in diameter, through which a jet of ink was blown on a recording paper. The system allowed recording frequencies up to 900 per sec.[5]

The system was calibrated by having the subject look back and forth between two lights 10° apart which were alternately lighted once per second. The amplication was adjusted so that an amplitude of 15 to 20 mm. on the recorded curve corresponded to an eye movement of 10° (Figure 2).

The procedure followed was first to calibrate the system for the subject. The spontaneous eye movements were recorded with the subject in a supine position, looking forward, and then with his head first in the right lateral and then in the left lateral position. In each position data were taken with eyes both closed and open. Recordings were also made in a supine position with open eyes looking forward and looking 35° to the right and to the left (lateral gaze). Each position was recorded for 60 to 90 sec. Recordings were made before the administration of a drug or alcohol and at regular intervals thereafter of 30 to 40 min. for a total of between 7 and 24 hr.

Nystagmus was defined as an eye movement consisting of a rapid and a slow component, the direction being defined as the direction of the rapid component (see Figures 3 and 5, below). Roving ocular movements were defined as rather slow horizontal eye movements, with the same speed in both directions, the actual record showing a sinuslike pattern (see Figure 8, below).

The recordings were evaluated in various ways:

Frequency was assessed by determining the average number of nystagmus beats or roving movements per second during the whole recording for 60 to 90 sec. in each position.

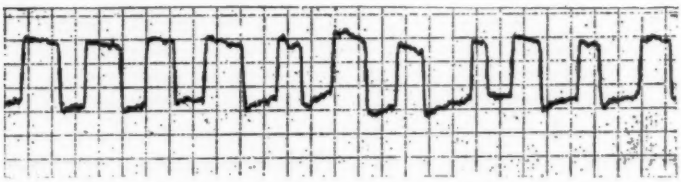

FIGURE 2.—*Calibration of Electrooculographic Recordings of Horizontal Eye Movements.* Subject looks alternately at two lights, 10° apart. Ordinate: amplitude = 5 mm. per square (15 mm. on recorded curve = 10° of eye movement). Upward stroke: eye movement to the right. Downward stroke: eye movement to the left. Abscissa: time = 0.5 sec. per square.

[5] The apparatus used, a Mingograph, was constructed by "Elema," Stockholm, Sweden.

Amplitude was ascertained by measuring the height of the nystagmus beats or roving movements on the recording charts in millimeters. These values were then expressed as degrees of eye movement by calibration.

Velocity of the eye movements, expressed in degrees per second, was obtained by dividing the sum of the amplitudes by the total time recorded. In discussions of nystagmus, velocity corresponds to the velocity of the slow component. Details regarding the recording have been reported previously (11, 13, 16).

Standing Steadiness

Standing steadiness was assessed by measuring the time the subject could stand with closed eyes (*a*) with one foot before the other (modified Romberg position) and (*b*) on the right and left feet respectively, 1 min. being set as the maximal value. The test was repeated at regular intervals during the experiments.

Electroencephalography (EEG)

EEG recordings were evaluated according to alpha frequency per second, alpha-percentage—expressed as percentage of alpha waves in total recording—and voltage. The results of the EEG findings will be reported in another communication.

Alcohol Administration

Alcohol was administered in three different ways: (*a*) Single dose administration so that absorption, distribution and disappearance of alcohol could be followed and related to the signs and symptoms evaluated; (*b*) Multiple dose administration with doses spaced so as to maintain a constant blood alcohol level; (*c*) Multiple dose administration with large doses spaced to obtain a constantly rising blood alcohol curve, administration being stopped when specific signs became positive.

A number of different beverages were used, ranging from distilled spirits and fortified wines to light wines and various kinds of beers. The alcohol content of the different beverages was analyzed and the amount of alcohol to be administered was calculated in proportion to body weight. The results of these studies will be published elsewhere.[6]

Samples for blood alcohol analysis (capillary blood) were taken in specially prepared glass capillaries ad modum Widmark (containing 0.1 ml. of blood). Samples were taken in triplicate at regular intervals, usually every 30 to 40 min., for 5 to 7 hr. in single dose experiments and for as long as 18 hr. in multiple dose experiments. Blood alcohol was analyzed by the Widmark dichromate sulphuric acid micromethod (1932). In some instances it was checked by the enzymatic alcohol dehydrogenase micromethod. The standard error of a triple sample,

[6] GOLDBERG, L. [In preparation.]

analyzed by either of these methods, was 0.025 mg. of alcohol per ml. of blood.

The blood alcohol curve was evaluated according to height and time of maximal value, distribution coefficient (r), rate of disappearance (β) and total amount of alcohol disappearing per time unit ($\beta \cdot r \cdot 60$), all factors being calculated from the values found by the method of least squares.

Drugs

A large number of drugs, including antihistamines, tranquilizers and sedatives, were tested. The drugs were given before or after the administration of alcohol. In a number of experiments drugs were administered several times at fixed intervals (usually 4 hr. apart).

In the experiments reported here, buclozine (50 + 50 mg.), chlorpromazine (10 + 10 mg.), hydroxyzine (25 + 25 mg.), meprobamate (400 + 400 mg.) and phenoglycodole (300 + 300 mg.) were given orally.

The experiments were designed as double-blind studies. Code numbers were used in administration and several placebo preparations were included.

Results

I. Alcohol

A. *Effects of a Single Dose of Alcohol*

Under normal conditions small and irregular eye movements only are seen on EOG, the amplitude as a rule being between 1° and 2° with either open or closed eyelids.

Positional alcohol nystagmus phase I (PAN I): Between 30 and 60 min. after the ingestion of a single dose of alcohol, a positional alcohol nystagmus is seen, beating with the rapid phase to the right when the head is in the right lateral position, changing its direction and beating to the left in the left lateral position. A typical record of PAN I is shown in Figure 3.

The frequency of PAN usually varies between 0.5 and 2 beats per sec., the amplitude between 2° and 20° per beat, and the velocity of the slow phase between 2° and 10° per sec. PAN is usually most intense in the lateral positions behind closed eyelids and much weaker or absent in the other positions recorded. Opening the eyes in any of the positions usually reduces the intensity of the nystagmus and may at low intensities block it completely (Figure 4).

Phase I lasts for 3 to 4 hr. and then disappears. (Typical diagrams of its intensity and duration are given below in Figure 7.)

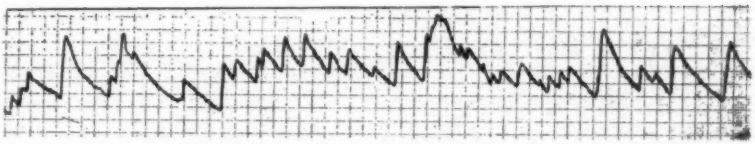

FIGURE 3.—*Electrooculographic Recording of Positional Alcohol Nystagmus, Phase I* (PAN I). Record shows horizontal nystagmus with rapid component beating to the right. Subject in supine position, head turned to the right (right lateral position) with eyes closed. Recording made 52 min. after ingestion of 0.7 g. of alcohol per kg. Blood alcohol level at time of recording: 90 mg. per 100 ml. Amplitude: 5.5° per beat. Frequency: 0.95 beats per sec. Velocity: 5.2° per sec. Upward stroke: eye movement to the right. Downward stroke: eye movement to the left. Calibration: 10 degrees = 15 mm. (1 square = 5 mm.). Time: 1 square = 0.5 sec.

Intermediate period: For 1 to 2 hr. following phase I, i.e., 4 to 6 hr. after the ingestion of a single dose of alcohol, no nystagmus can be recorded in any of the positions, with open or with closed eyes. (See Figure 7 below.)

Positional alcohol nystagmus phase II (*PAN II*): About 5 or 6 hr. after the ingestion of a single dose of alcohol, a second phase of positional alcohol nystagmus appears, now beating in the opposite direction, i.e., with the rapid phase to the left in the right lateral position, and to the right in the left lateral position. A typical record of PAN II is shown in Figure 5.

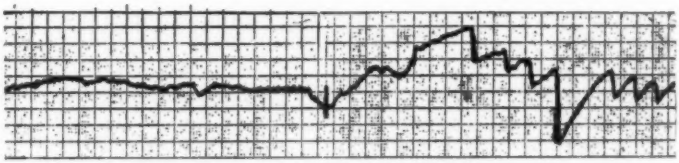

FIGURE 4.—*Electrooculographic Recording Showing Effect on Positional Alcohol Nystagmus of Opening and Closing the Eyes.* Horizontal recording of eye movements with subject in supine position, head turned to the right (right lateral position), 8½ hr. after ingestion of 0.7 g. of alcohol per kg. Blood alcohol level at time of recording: 0. Left portion shows record made while subject's eyes were open. Vertical stroke near center marks point when subject's eyes closed. Right portion shows nystagmus with rapid component beating to the left beginning 4.5 sec. after eyes closed. Amplitude: 6.2° degrees per beat. Frequency: 1.1 beats per sec. Velocity: 6.8° per sec. For other details see Figure 3.

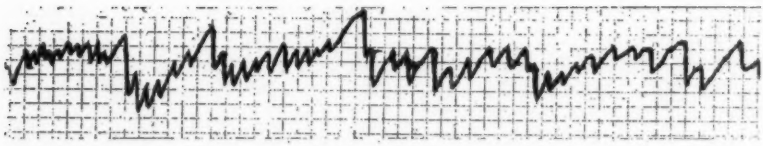

FIGURE 5.—*Electrooculographic Recording of Positional Alcohol Nystagmus, Phase II* (PAN II). Record shows horizontal nystagmus with rapid component beating to the left. Subject in supine position, head turned to the right (right lateral position) with eyes closed. Recording made 9 hr. after ingestion of 0.7 g. of alcohol per kg. Blood alcohol level at time of recording: 0. Amplitude: 2.1° per beat. Frequency: 2.0 beats per sec. Velocity: 4.2° per sec. For other details see Figure 3.

Phase II begins while the blood alcohol level is declining or, in some cases, after all alcohol has left the blood. It lasts for between 5 and 15 hr.—in every single case for several hours after the alcohol has disappeared from the blood.

Correlations: Typical diagrams showing the intensity and duration of phases I and II and their relation to the blood alcohol curve after single doses of alcohol can be seen below in Figure 7. The intensity of PAN varies between individuals. It is positively correlated with the amount of alcohol given. An increase in dose also increases the duration of phase II. However, the duration of phase I and of the latency periods preceding phases I and II are independent of the amount of alcohol ingested.

B. Effects of Multiple Doses of Alcohol

Administration of multiple doses of alcohol, spaced so as to maintain a more or less constant blood alcohol level, affects both the direction and intensity of PAN. Phase I may be prolonged for 5 to 8 hr., show a normal duration, last for a short time only, or appear in several distinct periods. In some cases when phase I is of short duration the intermediate period is prolonged for many hours. Phase II, also, may be very prolonged or appear in several distinct periods. In all cases, however, a long phase II is seen some hours after the ingestion of alcohol has stopped, when the blood alcohol curve is definitely declining.

It is hypothesized that a rising blood alcohol level induces PAN I after a short latency period (30 to 60 min.) and a declining blood alcohol level induces PAN II after a longer latency time. These induced nystagmus forms—whether phase I or phase II—are then

added with their "sign," i.e., the direction of their beats, to an already existing alcohol nystagmus. If induced and existing nystagmus have the same sign the result is a more intense and prolonged nystagmus. If, however, the induced and existing nystagmus beat in opposite directions, the result is a reduced nystagmus or none at all. This hypothesis would explain the mixed and apparently irregular picture of PAN after multiple doses of alcohol.

C. Subjective Symptoms

PAN was accompanied by a number of subjective symptoms, mainly headache, dizziness, vertigo and diplopia, and sometimes nausea or vomiting. The occurrence and intensity of these symptoms varied considerably among individuals. A comparison between the intensity of the nystagmus recorded and the intensity of the subjective symptoms makes it seem likely that there is a threshold value of recorded nystagmus that must be surpassed before subjective symptoms are felt. This threshold varies considerably from individual to individual. The symptoms reach their peak intensity when the objective EOG recordings show maximal intensity, i.e., 1 to 2 hr. after single dose ingestion (phase I) and 8 to 10 hr. after single dose ingestion (phase II).

II. Hangover

A number of symptoms experienced during the late stage after alcohol consumption, i.e., headache, dizziness, vertigo, nausea and sometimes vomiting, form part of the hangover syndrome.

In these experiments it has been demonstrated that PAN II corresponds in time to the hangover phase, starting 5 to 6 hr. after the ingestion of a single dose of alcohol and lasting for 5 to 10 hr. or longer, always several hours after all alcohol has disappeared from the body. It is therefore tempting to form a working hypothesis to the effect that PAN II is the objectively recorded correlate to the subjective hangover syndrome.

If this hypothesis is true, the administration of agents having an effect on the subjective symptoms of hangover should also influence the objectively measurable intensity of PAN II and possibly of PAN I.

Effect of a new alcohol dose: Administration of a new dose of alcohol during phase II has a very clear-cut effect on the recordings whether the blood alcohol curve is still declining or all alcohol has already left the body. The existing phase II changes within minutes

—the exact time depending on the amount of alcohol taken—and may be reduced in intensity, completely abolished, or reversed into phase I.

After 3 to 4 hr. the situation changes again, and the new phase I may be reversed again into a phase II, or the depressed phase II may increase in intensity. This final phase II usually lasts for some hours more than the original phase II.

A typical record is shown in Figure 6. In the experiment illustrated, the first dose of alcohol elicited PAN I and PAN II. A second dose, given after the alcohol from the first dose had disappeared from the blood, while PAN II was at its peak, eliminated the PAN II and changed it to PAN I which lasted 80–90 min. PAN II then reappeared. Since the second alcohol dose results in an initial rise in the blood alcohol level, the hypothesis stated above could explain the reappearance of phase I. When the second alcohol dose, after a latency time of 5 to 6 hr., induces a PAN II, this new phase II will be

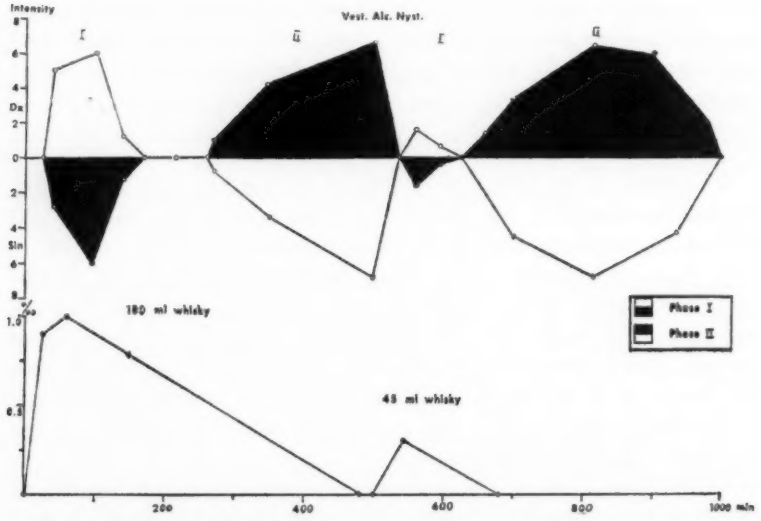

FIGURE 6.—*Time Course, Velocity and Direction of PAN after New Alcohol Doses in the Hangover Phase.* Horizontal electrooculographic recording of subject in supine position with eye closed, head in right lateral position (Dx) and left lateral position (Sin). Abscissa: time during experiment. Lower ordinate: blood alcohol concentration in mg. per 100 ml. First dose: 180 ml. of whisky (0.9 g. of alcohol per kg.) at 0 time. Second dose: 45 ml. of whisky (0.23 g. of alcohol per kg.) at 520 min. Upper ordinates: velocity of PAN in degrees per second.

added to an existing but suppressed phase II from the first alcohol dose. During the suppression of phase II by the new alcohol dose existing hangover symptoms, vertigo, dizziness and nausea, will disappear. When PAN II returns the subjective symptoms will return too.

III. Effect of Various Beverages

A large body of data has made it clear that different alcoholic beverages, containing equal quantities of absolute alcohol, do not produce identical blood alcohol levels when ingested. Distilled spirits give the highest levels, fortified wines somewhat lower ones, light wines still lower and beers the lowest.

Experiments have been carried out to determine whether the occurrence of nystagmus and hangover symptoms is the same or differs from beverage to beverage.

Typical results are shown in Figure 7. Equal amounts of alcohol (0.7 g. per kg.) were ingested during 30-min. periods—in one experiment as whisky (41 per cent by volume), in the other as beer (3.5 per cent by volume). In the whisky experiment, PAN I lasted for 165 min. with a velocity of 4.8° per sec.; PAN II lasted for 550 min. with a velocity of 3.2° per sec. In the beer experiment, on the other hand, the blood alcohol curve was much lower and so were the velocity and duration of PAN. PAN I lasted for 100 min. with a velocity of 2.6° per sec.; PAN II lasted for 300 min. with a velocity of 2.8° per sec. Further experiments are being carried out to determine whether these differences are due only to variations in blood alcohol levels or to other factors specific for each type of beverage.

IV. Roving Ocular Movements

A. General Description

Now and then during electrooculographic recordings slow, regular, roving ocular movements (ROM) are seen, the eyes moving horizontally from side to side with the same velocity to the right and to the left. These ocular movements are usually observed only when the eyes are closed. The EOG recordings of these slow roving movements show a sinuslike pattern (Figure 8). The amplitude for a complete revolution (left + right) usually varies between 2° and 25° with an average of 10° to 15°. The frequency varies between 2 and 6 sec. per one complete revolution, an average of 4 sec. per movement, which is considerably slower than nystagmus. The velocity is about 2° to 4° per sec.

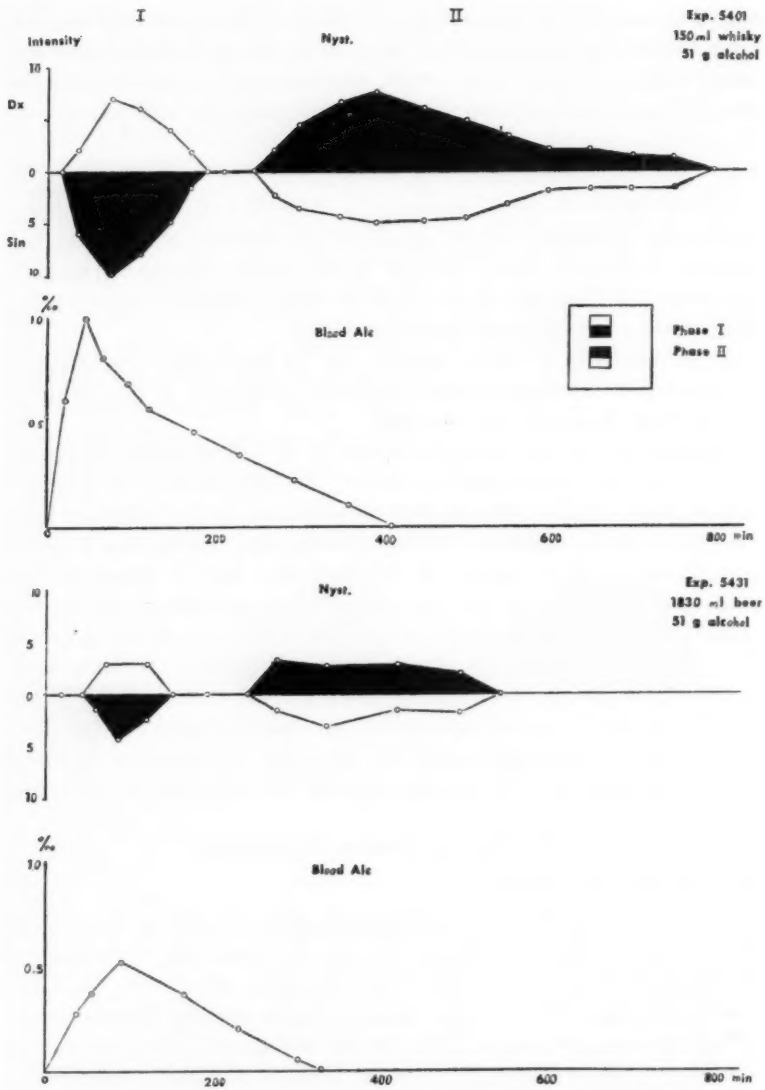

FIGURE 7.—*Comparison of Time Courses and Velocities of PAN after Ingestion of Equal Doses of Alcohol in Whisky and in Beer.* Electrooculographic recordings of eye movements of subject with eyes closed, head in right lateral position (Dx) and left lateral position (Sin). Abscissa: time during experiment. Lower ordinates: blood alcohol concentration in mg. per 100 ml. Dosage: 0.7 g. of alcohol per kg. Upper ordinates: velocity of PAN in degrees per sec.

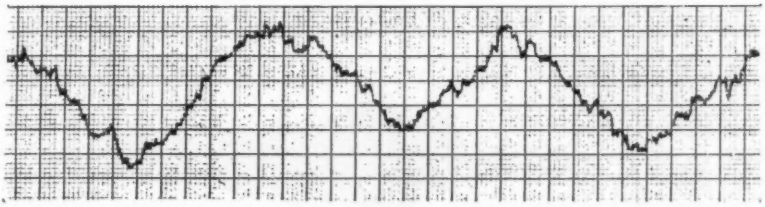

FIGURE 8.—*Electrooculographic Recording Showing Slow Horizontal Roving Ocular Movements.* Horizontal recording with subject in supine position, head in right lateral position with eyes closed. Recording made 3 hr. after ingestion of 0.7 g. of alcohol per kg. plus 0.8 g. of meprobamate. Blood alcohol level at time of recording: 55 mg. per 100 ml. Amplitude: 15.0° per beat. Frequency: 0.19 beats per sec. Velocity: 2.9° per sec. For other details see Figure 3.

The roving movements sometimes appear before alcohol administration, usually in the supine position with closed eyelids. They are sometimes observed after alcohol administration, alternating with the regular PAN, usually in the supine and in the lateral positions behind closed eyelids. They are also sometimes seen after the alcohol has disappeared from the blood (Figures 9 and 10).

B. Correlation with Positional Alcohol Nystagmus

When a PAN is recorded no roving movements are seen. If during a recording roving movements appear, an existing positional nystagmus disappears and is not superimposed on the ROM.

It appears that the appearance of ROM suppresses a possible positional nystagmus, both phase I and phase II; when the roving movements disappear, the suppressed PAN may reappear. This can be seen to occur within seconds on a recording; periods of nystagmus and roving movements may alternate with each other.

These findings indicate a certain interplay between nystagmus and roving movements. When the mean intensity of the PAN induced by a given alcohol dose—whether phase I or phase II or both—is plotted against the mean intensity of the subject's ROM during the same time period, a clear negative correlation is seen: the intensity of the nystagmus decreases with an increase in the intensity of the roving movements (Figures 9 and 10).

C. Subjective Symptoms

The subjective symptoms associated with intense ROM are primarily drowsiness, sleepiness and tiredness; in some cases the ROM

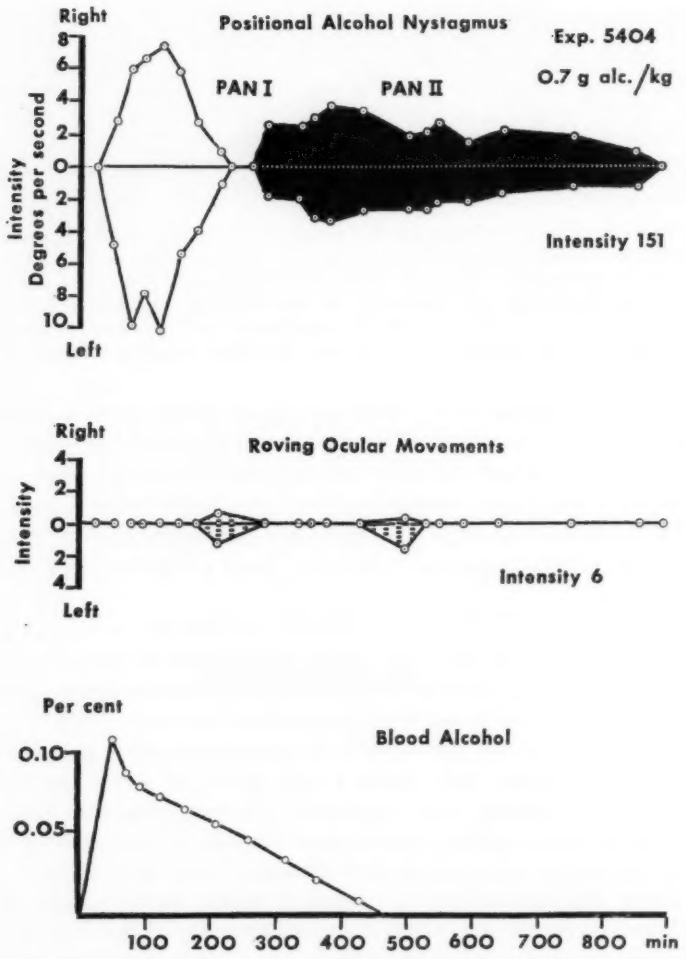

FIGURE 9.—*Comparison of PAN, ROM and Blood Alcohol Concentrations following Ingestion of Alcohol plus Placebo.* Horizontal electrooculographic recording of subject in supine position with eyes closed, head in right and left lateral positions. Dosage: 0.7 g. of alcohol per kg. + placebo. Upper curve: intensity of PAN. Middle curve: intensity of ROM. Lower curve: blood alcohol concentrations. Values for PAN I, PAN II and ROM, respectively: amplitude—5.0°, 2.0° and 1.6° per beat; frequency—1.1, 1.2 and 0.25 beats per sec.; mean velocity—5.6°, 2.4° and 0.4° per sec.; duration—150, 600 and 225 min. Total intensity of PAN and ROM (in arbitrary units): 151 and 6, respectively.

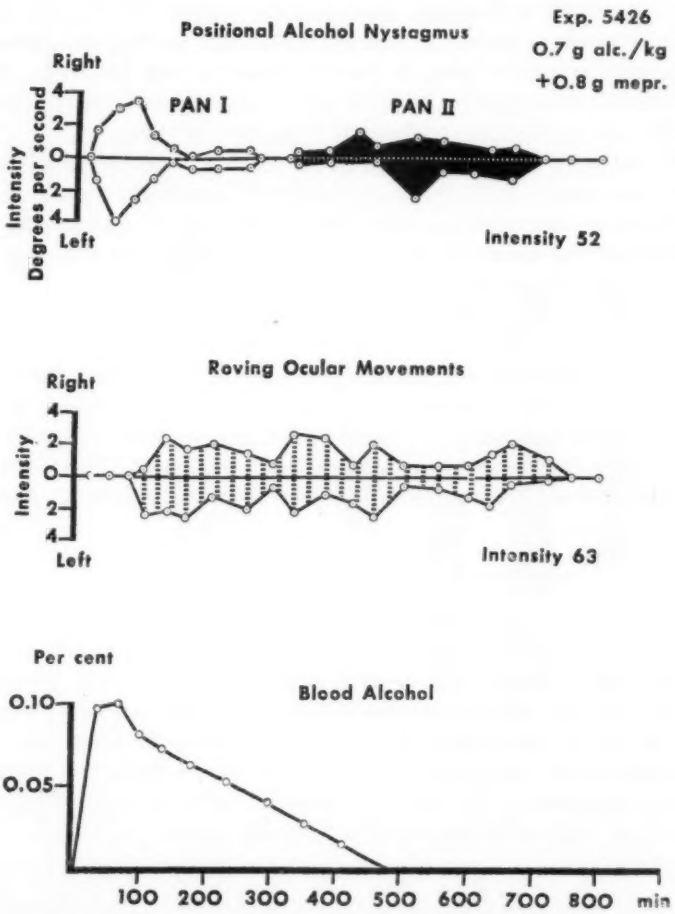

FIGURE 10.—*Comparison of PAN, ROM and Blood Alcohol Concentrations following Ingestion of Alcohol plus Meprobamate.* Horizontal electrooculographic recording of subject in supine position with eyes closed, head in right and left lateral positions. Dosage: 0.7 g. of alcohol per kg. + 0.8 g. of meprobamate. Upper curve: intensity of PAN. Middle curve: intensity of ROM. Lower curve: blood alcohol concentrations. Values for PAN I, PAN II and ROM, respectively: amplitude—1.2°, 1.0° and 8.3° per beat; frequency—1.2, 1.1 and 0.24 beats per sec.; mean velocity—1.4°, 1.1° and 2.0° per sec.; duration—200, 370 and 675 min. Total intensity of PAN and ROM (in arbitrary units): 52 and 63, respectively. Reduction of PAN from alcohol + placebo: 44 per cent. Increase of ROM from alcohol + placebo: 15 times.

were associated with sleep. Arousing the subject by having him count or answer questions usually makes the roving movements disappear for a short time if their intensity is not too high. The occurrence and intensity of ROM varies considerably among individuals and in the same individual from time to time.

The subject's degree of alertness seems to be one decisive factor in the occurrence of ROM. During hangover, especially if recordings are made on the morning after alcohol was taken, an increase in occurrence and intensity of ROM and a corresponding decrease in the intensity of PAN II are seen.

V. Effect of Heat and High Humidity

Room temperature and humidity also affect the relation between PAN and ROM. An increase in temperature and in humidity seems to induce the appearance of more or less intense ROM, followed by an increase in tiredness, drowsiness and sleepiness. This pattern is accompanied by a corresponding decrease in the intensity of both PAN I and PAN II.

VI. Effect of Alcohol plus Tranquilizers

In a number of cases therapeutic doses of the drugs tested brought about no specific changes from normal in the EOG recordings, especially no nystagmus. A more constant level, i.e., less irregular eye movements, was not unusual. Some of the tranquilizers induced ROM in cases where these movements did not exist before the administration of the drugs, or intensified the velocity of existing roving movements. The administration of various drugs interfered in several ways with the effects of alcohol alone.

EOG recordings: After ingestion of some drugs, mainly buclozine, chlorpromazine, hydroxyzine, meprobamate and phenoglycodole, PAN I and PAN II were both either reduced or suppressed, compared with the findings after ingestion of alcohol alone (Figure 11). ROM appeared and their intensity and duration were considerably greater than the occasional movements seen after alcohol alone.

After drug plus alcohol ROM in many cases lasted for hours after alcohol had disappeared from the blood and were accompanied by subjective feelings much more severe than after alcohol alone. The drowsiness and tiredness were very marked—to the extent that some subjects had difficulty in performing their experimental tasks. Some of them even slept for quite a time during the actual experiment;

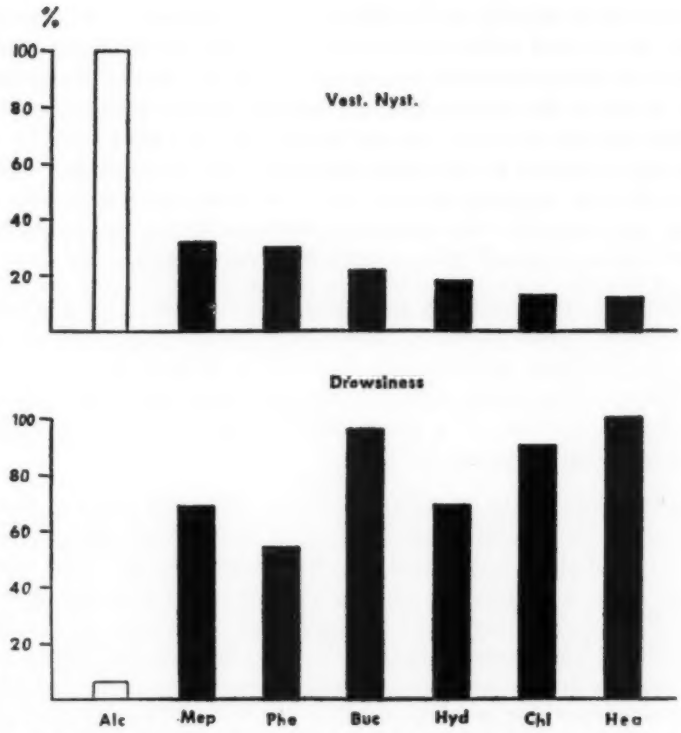

FIGURE 11.—*Comparison of Effects of Administration of Alcohol plus Various Tranquilizers on PAN and ROM.* UPPER FIGURE: intensity of PAN after administration of alcohol with placebo and with various tranquilizers. Ordinate: 100 per cent = level of intensity of PAN after alcohol + placebo. LOWER FIGURE: intensity of ROM (degree of drowsiness is proportionate to intensity of ROM) after administration of alcohol with placebo and with various tranquilizers. Ordinate: 100 per cent = level of intensity of ROM after alcohol + "heat" (see definition below), the highest intensity observed. All values are averaged from five experiments. Abbreviations: Alc = alcohol + placebo. Mep = meprobamate. Phe = phenoglycodole. Buc = buclozine. Hyd = hydroxyzine. Chl = chlorpromazine. Hea = "Heat" (increase in room temperature to 81°F and in relative humidity to 90 per cent).

this did not occur after the same dose of alcohol without drug, or occurred only for short periods of time.

In these experiments as in those with alcohol alone there seemed to be a correlation between the intensity of PAN and that of ROM.

Plotting mean intensity of alcohol nystagmus (phase I + II) against mean intensity of roving movements, from records of effects of the various drugs plus alcohol, shows a negative correlation, the nystagmus intensity decreasing with an increase in the intensity of the roving movements. This correlation can also be seen in Figure 11. The upper portion of the figure shows how the tranquilizers tested decreased the intensity of PAN from the value associated with alcohol plus placebo. The matching columns in the lower portion show a clear increase in ROM with each decrease in PAN.

Standing steadiness: In most cases when a drug plus alcohol was administered standing steadiness showed more impairment at a given blood alcohol level than when alcohol alone was administered. The results also showed that impairment in standing steadiness appeared at a lower blood alcohol level after alcohol plus drug than after alcohol alone.

Comparison between different drugs: The experiments clearly show that the combined effect of drug plus alcohol changes with the kind of drug tested and the dose administered. Some drugs bring about a suppression of PAN, an increase in intensity of ROM, a feeling of drowsiness and tiredness and a decrease in standing steadiness. Some seem to have little effect on PAN but induce ROM and corresponding symptoms. Others suppress PAN more and interfere to a lesser degree with standing steadiness. These studies have shown that tranquilizing agents and central nervous system depressant drugs potentiate the effect of alcohol.

Studies are under way to determine whether there may be specific drugs that will selectively suppress PAN and its associated symptoms (vertigo, dizziness and nausea) without inducing ROM with their associated states (drowsiness, tiredness and sleepiness) and without impairing standing steadiness (coordination).

DISCUSSION

The relationship demonstrated above between the degree of drowsiness of a subject and the occurrence and intensity of ROM, as well as the fact that certain tranquilizing agents, alone or combined with alcohol, increase the intensity of ROM, make it likely that the site of the interaction between alcohol and tranquilizers is in the reticular system.

The findings that PAN and ROM continue to occur as objective

aftereffects of drinking even after alcohol has disappeared from the blood may serve as a model to help in the understanding of acute withdrawal symptoms occurring after prolonged alcohol intake.

The hypothesis presented earlier to explain how the administration of additional alcohol may counteract the objective central nervous system changes and the subjective symptoms originally induced by the ingestion of the same drug, may help also in understanding how a craving to continue taking a drug is perpetuated in alcoholics.

It seems probable that experiments of this kind, especially if based on a number of objective recordings of central nervous system functions, can serve to clarify the underlying mechanisms of synergism, potentiation and antagonism in the central nervous system and contribute to an understanding of the mechanisms and sites of action of centrally active drugs, especially those specifically aimed at the treatment of alcoholism.

Summary

Experiments are described using electrooculography, electroencephalography and measurements of standing steadiness, to study acute effects of alcohol and tranquilizers in the central nervous system, both immediately following alcohol intake and during hangover, in 80 healthy men. Two main ocular movements were studied: a horizontal positional alcohol nystagmus (PAN), and horizontal roving ocular movements (ROM).

1. Alcohol induces two phases of PAN separated by an intermediate period of 1–2 hours: PAN I lasts 3–4 hr. during alcohol intake; and PAN II lasts 5–15 hr. and continues after alcohol has left the blood.

2. PAN II is connected with hangover, i.e., it is associated with symptoms of dizziness, vertigo, nausea and vomiting. A hypothesis explaining the effect on PAN of alcohol intake during the hangover phase is proposed.

3. Ingestion of equal amounts of alcohol in various alcoholic beverages results in differences in the intensity and duration of effects and aftereffects as shown, e.g., by the differences in intensity of PAN and of ROM. The differences are correlated with differences in blood alcohol levels.

4. ROM accompanied by subjective symptoms such as tiredness, drowsiness and sleepiness were recorded during and after alcohol intake as objective aftereffects.

5. Increase in room temperature and humidity increases the intensity of ROM.

6. After administration of alcohol plus tranquilizing drugs PAN is usually reduced and ROM proportionally increased in intensity.

7. These findings may serve to elucidate the mechanism underlying acute withdrawal symptoms and craving for alcohol in alcoholics.

REFERENCES

1. JOFFROY, A. and SERVEAUX, R. Mensuration de la toxicité vraie de l'alcool éthylique; symptomes de l'intoxication aigüe et de l'intoxication chronique par l'alcool éthylique. Arch. Méd. exp. **9**: 681–707, 1897.
2. BÁRÁNY, R. Experimentelle Alkoholintoxikation. Mschr. Ohrenheilk. **45**: 959–962, 1911.
3. BÁRÁNY, R. and ROTHFELD, J. Untersuchungen des Vestibularapparates bei akuter Alkoholintoxikation und bei Delirium tremens. Zbl. Nervenheilk. **50**: 133–158, 1913.
4. BERNHARD, C. G. and GOLDBERG, L. Nystagmus spontane par suite d'intoxication aigüe par l'alcool. Acta med. scand. **84**: 36–44, 1934.
5. DE KLEYN, A. and VERSTEEGH, C. Experimentelle untersuchungen über den sogenannten Lagenystagmus während akuter Alkoholvergiftung beim Kaninchen. Acta oto-laryng., Stockh. **14**: 356–377, 1930.
6. NYLÉN, C. O. Positional nystagmus: Review and future prospects. J. Laryng. **64**: 295–318, 1950.
7. FRENZEL, H. Alkohollagenystagmus beim Menschen. Arch. Ohr.- Nas.-, u. KehlkHeilk. **146**: 220–222, 1939.
8. PLENKERS, J. Ueber Lagenystagmus während akuter Alkoholintoxikation beim Menschen. Arch. Ohr.- Nas.-, u. KehlkHeilk. **152**: 197–206, 1943.
9. WALTER, H. W. Alkoholmissbrauch und Alkoholnystagmus. Dtsch. Z. ges. gerichtl. Med. **43**: 232–241, 1954.
10. ASCHAN, G., BERGSTEDT, M., GOLDBERG, L. and LAURELL, L. Alkohollägenystagmus. Trans. swed. otol. Soc. (Dec. **4**, 1955) **1**: 39–43, 1955.
11. ASCHAN, G., BERGSTEDT, M., GOLDBERG, L. and LAURELL, L. Positional nystagmus in man during and after alcohol intoxication. Quart. J. Stud. Alc. **17**: 381–405, 1956.
12. ASCHAN, G. Different types of alcohol nystagmus. Acta oto-laryng., Stockh., Suppl. 140, pp. 69–78, 1958.
13. ASCHAN, G., BERGSTEDT, M. and GOLDBERG, L. The effect of some antihistaminic drugs on positional alcohol nystagmus. Acta oto-laryng., Stockh., Suppl. 140, pp. 79–90, 1958.
14. ASCHAN, G., BERGSTEDT, M. and GOLDBERG, L. Effects and Aftereffects of Alcohol on the Vestibular Nerve. [Swedish.] Presented at the Swedish Medical Society, 24 Jan. 1956.
15. GOLDBERG, L. Metabolism and action of alcohol. Long-term studies on acute and chronic effects in man. Proc. 26th internat. Cong. Alc. Alcsm, Stockh. (August 1960). [In press.]
16. ASCHAN, G., BERGSTEDT, M. and STAHLE, J. Nystagmography. Acta oto-laryng., Stockh., Suppl. 129, 1956.

The Etiology of Alcoholism

Ebbe Curtis Hoff, Ph.D., M.D.[1]

THE ETIOLOGY of alcoholism is far from perfectly understood and this lack of understanding creates major difficulties in establishing specific therapeutic and preventive approaches (1). The first essential step in discussing etiology must be definition of terms. While alcoholism is variously defined, we may accept for the purposes of this discussion at least three basic definitive elements: First, there is a loss of control of alcohol intake, an essential symptom, signalling the onset of clinically discernible alcoholism. The victim finds himself drinking when he intended not to drink and drinking more than he has planned. Second, there is functional or structural damage. This damage may be physiological, psychological, domestic, economic, social, or, frequently, a combination of several of these. This harm is presumably caused by unusual poisonous effects of alcohol acting directly or indirectly upon the alcoholic. There are reasons to believe, however, that in the alcoholic some pathological process develops, possibly in the brain, a process which continues whether or not alcohol is consumed. An alcoholic who remains abstinent for many years, for example, will find that if he begins to drink again alcohol will have just as devastating effects as before and possibly even more harmful ones. The third criterion in this definition of alcoholism centers around the clinical fact that an alcoholic uses alcohol to try to satisfy abnormal needs. Alcohol becomes for him a kind of universal therapy—a psychopharmacological substance through which he attempts to keep his life from disintegration. He uses alcohol to give him courage, to escape from intolerable decisions, to tranquilize his nervousness, to give a sense of meaning to life. The abnormal alcohol use is, in fact, an attempt—usually unrecognized—to handle intrapsychic problems and life situations.

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One etiological theory that must be discussed is that alcoholism is simply self-imposed habitual indulgence. While recognized formally by most people as archaic, this theory nevertheless persists in so-called commonsense thinking and action. The behavior of the alcoholic reinforces the conviction of many people that the alcoholic could really stop drinking if only he mobilized his "will-power" sufficiently. Another consideration that contributes to the indulgence theory is the belief that prolonged or heavy drinking leads to alcoholism. Actually, this has never been satisfactorily established as a sole or even primary cause of alcoholism. Nevertheless, because of these beliefs, feelings of blame and hostility are often directed toward the alcoholic and the alcoholic himself feels guilty and remorseful. The mechanism of loss of control is not understood. Outmoded psychological concepts have in the past favored the view that this loss of control is a habit and the conditioned reflex treatment has its theoretical basis in an oversimplification of Pavlovian neuropsychology. The indulgence theory of alcoholism raises the important issue of the extent to which the victim of alcoholism is responsible for his condition, either after he becomes an alcoholic or in the prealcoholic stages of his drinking. The moral and theological questions involved here have been intelligently and precisely dealt with by Ford (2). The therapist can help the alcoholic patient to differentiate the moral issues from neurotic guilt feelings.

Attitudes toward the indulgence theory have an important effect on methods of treatment of alcoholics. If this view is accepted, therapeutic concern will be directed toward maintenance of abstinence through the willful rejection of alcohol at all costs. If the theory is not accepted, the therapist must use other methods of treatment and abstinence, while essential, will not be the only goal.

The modern approach to helping alcoholics is summarized in the slogan, "Alcoholism is a disease; an alcoholic is a sick person who needs and deserves help." This slogan is the focus of a vast controversial discussion and has not in fact found any single unqualified verification. Of course an alcoholic is manifestly sick when suffering from symptoms of alcohol intoxication or withdrawal. Moreover, there are so-called "diseases" of alcoholism such as peripheral neuropathy, cirrhosis of the liver, Wernicke's disease and Korsakoff's psychosis. Furthermore, an alcoholic's chronic nervousness, dependency, immaturity and frequent poor judgment give the im-

pression that even when sober (or perhaps especially when sober) he is unwell psychologically. Nevertheless, it is impossible to define alcoholism as an entity in terms of one etiology with characteristic medical and psychological pathology and a specific clinical course.

The Role of Alcohol

As has been stated, it is not yet possible to say to what extent alcohol itself is a cause of alcoholism. Most people who drink do not become alcoholics although they may drink consistently over a prolonged period. The drinking of alcohol may be thought of as a contingent cause but the mechanism is not known.

Alcoholism as a Symptom

In thinking of the disease concept of alcoholism it is reasonable to regard loss of control and abnormal drinking patterns as symptomatic of underlying etiological factors which may be multiple. It may even be contended that the choice of alcohol as an addictive modality is entirely fortuitous and that alcoholism ought not to be considered as an entity at all but should be approached simply from the point of view of presumed underlying disturbances. This concept in its extreme form may lead to a therapeutic practice abolishing special or specific considerations of the alcoholic as such.

Psychological Factors

Most psychological theories of the genesis of alcoholism stem from the experience of professional observers who usually see those patients revealing clear-cut prealcoholic personality and behavioral disorders and that fit into psychiatric diagnostic categories. The best formulated psychological theories are based on the concept that psychological functions are related to physiological functions in a biosocial organism (3, 4). To the psychologist and the psychiatrist the alcoholic's uncontrolled use of alcohol is symptomatic of preexistent psychological defect. The alcoholic demands more from alcohol than do other drinkers. In fact, he may accurately be said not to "drink" in the ordinary social sense but really to "inject" himself with alcohol as if it were a medicine.

In cases where an alcoholic gives a history of trouble with alcohol almost from the first drink it is obvious that alcohol use was not a precurrent factor in the problem. It could, of course, be said in

such cases that the individual was from the start physiologically unable to handle alcohol safely but it is equally likely that alcoholism of early onset originates in the finding by a psychologically sick person of a substance with desired psychopharmacological effects.

On the other hand, some alcoholics give a clinical history of years of apparently unharmful controlled drinking. Even in these instances, however, one often discerns a characteristically high tolerance of alcohol. These patients will tell the examiner that for years they could "drink their friends under the table" and "get away with it." Some of them never knew what it was to have a hangover even after an evening of heavy drinking. While such persons remained relatively well-integrated during this period of high tolerance, it seems likely that in many there were pathological features and that alcohol played an abnormal psychological role from the start. Just how the central nervous system was able to deal with the onslaught of such amounts of alcohol is hard to know. For many such patients the onset of alcoholism was identified in the patient's experience by a gradual fall in tolerance. This tolerance factor seems to be related to alcoholism in some ways but just what the psychological and neurological bases for it are is not clear. Tolerance of alcohol intake is affected on specific occasions by emotions and emotional factors may be implicated in this long-term change.

An important consideration in psychological theories of alcoholism is the question of the specificity of the etiological determinants. The possibility that the prealcoholic personality may present a characteristic psychological picture has been explored extensively but at present there is no agreement as to a single determinant or group of determinants (5). It is true that alcoholics are seen as sexually immature, dependent, inadequate and having low tolerance for pain and for unwanted feelings. Some of these characteristics, however, may be results rather than causes of the complicated developmental processes of the disease. For example, dependency in the alcoholic has been characterized as an undue reliance upon environmental fields. While the nonalcoholic in the face of conflicting stimuli in an experimental situation relies more upon proprioceptive stimulation, the alcoholic preferentially responds to sensory stimuli from the visual field (6). This has been demonstrated in a variety of experiments and it seems likely that this is a prealcoholic characteristic of these patients rather than an outcome

of the disease. While further work in this area is desirable, it may be hypothesized that at least in some alcoholics some disturbance during the first few years of life may have interfered with reliance upon the developing proprioceptive system and the antigravity reflexes.

Alcoholics have been said to have a low tolerance of tension. It seems quite likely that the tension of many alcoholics—from whatever psychological or neurological cause—is affected by significant hormonal disturbances. The impact of even a relatively small excess catecholamine activity, for example, can be very powerful (7). Neurophysiological research has revealed the significant jurisdiction exerted by the cortex and related higher cerebral levels upon autonomic functions and is confirming the hypothesis that these cortical autonomic mechanisms may generate psychosomatic symptoms usually associated with anxiety and tension (8, 9). Cortical stimulation mobilizes epinephrine activity, for example. Since these higher cerebral mechanisms depend upon the influence of the reticular activating system, the effects of alcohol and alcohol withdrawal on this system might profitably be studied in connection with the problem of etiology.

Many alcoholics are depressed—some probably from neurophysiological causes or with neurophysiological complications. This depression may be temporarily relieved by alcohol but the relief is succeeded by a period of enhanced depression during and following withdrawal. For these and other reasons many alcoholics are seen to suffer from intolerance of present reality. The sensitive leading edge of existence—the interface between the past and the future in which human beings must learn to live—is often unbearable for the alcoholic who seeks to escape from its pains and decisions and retreats into temporary self-oblivion. This chemical comfort-seeking may be exaggerated to the extent that the victim finds meaning in life in alcohol alone. In a real sense many an alcoholic has found in his alcoholism a kind of chemical religion (1).

Many childhood experiences have been specified as having psychological consequences that often lead to alcoholism. Early deprivation is an example (10). The inability to relate to others effectively resulting from this experience is often seen in alcoholics. The difficulty in adapting this knowledge to an etiological theory, however, is that many persons with psychological disabilities do not become alcoholics.

Sociocultural Factors

Sociocultural factors appear to be significantly related to the prevalence of alcoholism (11). Among these are attitudes towards drinking and drunkenness: recent studies correlate cultural acceptance of drunkenness with high alcoholism rates. Implicit in these observations, as applied to a social or cultural etiology, is the premise that alcohol use—either normal or deviant—may lead to alcoholism while so-called temperate use may reduce the likelihood of alcoholism. Sociocultural studies have provided highly intriguing leads and should be continued and expanded. Especially important is the development of more reliable direct methods of measurement of prevalence (12).

Physiological Factors

Physiological–metabolic theories of etiology seem to stand at the bottom of the list in order of obviousness. It seems probable, however, that such theories would be more likely than others to produce therapeutic advances. Physiological and biochemical investigation of alcohol metabolism and action in alcoholics and possible differences between these patients and nonalcoholics is highly important.

While psychological and sociocultural studies hold out great promise for the understanding of alcoholism in the long run, advances in psychological theories of alcoholism do not seem to promise early expansion of therapeutic effectiveness. Moreover, the sociocultural approach to the treatment and prevention of alcoholism involves such drastic, sweeping and generalized reforms of attitudes and practices in society that it seems utopian to hope that they will be carried out. The metabolic theories, on the other hand, suggest fairly specific even if difficult areas for study from which scientific data may be secured (13). The high tolerance to alcohol in the prealcoholic and the reduction of tolerance associated with his entry into his illness suggest many experiments. With more sophisticated techniques biochemists are likely to become increasingly able to identify any abnormal ways in which the body of the alcoholic deals with alcohol. It may well be that the breakdown of alcohol in the system of the alcoholic is different from that in the prealcoholic or the drinker who never becomes an alcoholic (14). Abnormalities in the metabolism of alcohol or its breakdown

products may be responsible for the unusually damaging effects of alcohol ingestion in some people and may have an abnormal effect on cellular metabolism in the prealcoholic. The central neurons may be disturbed in bizarre ways or there may be unusual effects upon synaptic transmission. The complex excitatory–inhibitory effects of alcohol on the nervous system (15) call for further study.

Brain Damage

Brain damage from long-continued alcohol use or from other causes could be the basis of the change in tolerance to alcohol suffered by some alcoholics and for memory "blackouts" as well as loss of ability to control alcohol intake. Emotional factors may play a role too. The heightened overactivity of central neurons following alcohol clearance, resulting in convulsions and visual and auditory hallucinations, may also be part of this picture. Brain damage may also be responsible for disturbances at the reticular level of higher cerebral mechanisms of autonomic and behavioral control. Thus it may be that stressful situations or internal stimuli create more severe autonomic disturbances in the alcoholic than in the normal person. Experiments in animals have shown that alcohol acts as an imperfect blocking agent for some cerebral autonomic effects such as cardiac arrhythmias (15). Alcohol is inferior to some other psychopharmacological agents in protecting the organism from the autonomic end-effects of cerebral stimulation.

Endocrinological Factors

As has been said, alcoholism has been ascribed to endocrine dysfunctions. The thyroid and adrenal glands have been implicated and hormone therapy has been attempted. The therapeutic use of leuco-adrenochrome is an important instance. Animal studies of genetic differences in individuals as predisposing to alcoholism (16) deserve further attention. It has recently been shown that strains of mice that prefer alcohol solutions to water reveal enzyme differences from those who do not. C57BL/6J mice, which prefer alcohol, have a higher level of liver alcohol dehydrogenase than do C3H control mice, and under conditions in which the alcohol solution is the only source of liquid, the C57BL/6J animals will ingest larger amounts of alcohol than the controls (17). While it is not yet possible to produce a clinical picture of alcoholism in experimental animals, alcohol preference studies do hold promise.

Further Research

Investigations of the etiological factors in alcoholism are of utmost importance to the search for effective therapies and preventive methods and deserve high priority. Further study is needed of alcohol metabolism and its effects, especially in relation to brain chemistry and functioning, to differences between alcoholics and nonalcoholics, and to differences in genetically differentiated strains of animals. Also essential are sociocultural studies of alcohol use, prevalence of alcoholism and attitudes about alcohol and alcohol problems. Finally, it is suggested that longitudinal psychobiological studies of human subjects be carried out to determine what chemical, psychological, social or cultural factors are etiologically related to alcoholism. Such studies, begun with young people and continued over a period of several years, seem to offer the most promising approach to the etiological problem.

Summary

Physiological, psychological, sociocultural, neurological and endocrinological factors in the etiology of alcoholism are described and discussed and suggestions for areas of further research are briefly outlined.

REFERENCES

1. Hoff, E. C. The alcoholic. In: Pike, E., ed. Who is My Neighbor?; pp. 63–80. Greenwich, Conn.; Seabury Press; 1960.
2. Ford, J. C. Depth Psychology, Morality and Alcoholism. Weston, Mass.; Weston College; 1951.
3. Alexander, F. Views on the etiology of alcoholism. *II*. The psychodynamic view. In: Kruse, H. D., ed. Alcoholism as a Medical Problem; pp. 40–46. New York; Hoeber-Harper; 1956.
4. Shoben, E. J., Jr. Views on the etiology of alcoholism. *III*. The behavioristic view. In: Kruse, H. D., ed. Alcoholism as a Medical Problem; pp. 47–55. New York; Hoeber-Harper; 1956.
5. Zwerling, I. Psychiatric findings in an interdisciplinary study of forty-six alcoholic patients. Quart. J. Stud. Alc. **20**: 543–554, 1959.
6. Witkin, H. A., Karp, S. A. and Goodenough, D. R. Dependence in alcoholics. Quart. J. Stud. Alc. **20**: 493–504, 1959.
7. Ferguson, R. W., Folkow, B., Mitts, M. G. and Hoff, E. C. Effect of cortical stimulation upon epinephrine activity. J. Neurophysiol. **20**: 329–339, 1957.
8. Hoff, E. C., Kell, J. F., Jr., Hastings, N., Sholes, D. and Gray, E. Vasomotor, cellular and functional changes produced in kidney by brain stimulation. J. Neurophysiol. **14**: 317–332, 1951.
9. Hoff, E. C. The brain—a master coordinator. Res. Rev. (Office of Naval Research, Dept. of the Navy), pp. 7–13, 1953.

10. Myerson, D. J. Clinical observations on a group of alcoholic prisoners. With special reference to women. Quart. J. Stud. Alc. **20**: 555–572, 1959.
11. Hollingshead, A. B. Views on the etiology of alcoholism. *IV*. The sociologic view. In: Kruse, H. D., ed. Alcoholism as a Medical Problem; pp. 56–60. New York; Hoeber-Harper; 1956.
12. Gordon, J. E. The epidemiology of alcoholism. In: Kruse, H. D., ed. Alcoholism as a Medical Problem; pp. 15–27. New York; Hoeber-Harper; 1956.
13. Himwich, H. E. Views on the etiology of alcoholism. *I*. The organic view. In: Kruse, H. D., ed. Alcoholism as a Medical Problem; pp. 32–38. New York; Hoeber-Harper; 1956.
14. Westerfeld, W. W. and Schulman, M. P. Some biochemical aspects of the alcohol problem. Quart. J. Stud. Alc. **20**: 439–451, 1959.
15. Carroll, M. N., Jr., Hoff, E. C., Kell, J. F., Jr. and Suter, C. G. The effects of ethanol and chlordiazepoxide in altering autonomic responses evoked by isocortical and paleocortical stimulation. Biochem. Pharmacol. **8**: 15, 1961.
16. Williams, R. J. Biochemical individuality and cellular nutrition: prime factors in alcoholism. Quart. J. Stud. Alc. **20**: 452–463, 1959.
17. Wilson, E. C. and Respess, J. C. A study of ethanol metabolism in mice which preferentially consume ethanol. Gastroenterology. [In press.]

The Alcohol Withdrawal Syndromes

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THIS PAPER is intended to give a brief review of the available neurophysiological data on alcohol withdrawal states, while major attention is directed to those clinical points which have been of most benefit in assessing and treating patients in withdrawal.

Neurophysiological Data

Although the signs of alcohol intoxication are well known, it is less well appreciated that if the blood alcohol level is kept more or less constant, the subject will gradually regain his preintoxication state of motor and mental functioning (1, 2). Further, it has been demonstrated that intoxication is more apparent when the blood alcohol concentration is rising than when it is falling.[2] If one further examines this peculiar adaptability of the central nervous system and confines his attention to the descending limb of the blood alcohol curve, still another phenomenon becomes apparent. This is the increased excitability seen in the habituated individual. McQuarrie and Fingl (4), using ethanol in dosage sufficient to produce depression in cortical response to electrical and chemical convulsive stimuli, were able to show that when the alcohol effect had waned there was a period of hyperexcitability which was related to the duration of prior medication. Thus, 7 hours after a single dose of ethanol there was increased susceptibility to convulsions. This susceptibility was maximal at 8 hr. and finally disappeared completely after 23 hr. On the other hand, animals treated with alcohol for 14 days and then suddenly withdrawn from alcohol showed maximal hyperexcitability on the second day but this did not subside until an entire week had elapsed. It would appear that such hyperexcitability is the experimental equivalent

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[2] Mellanby (3), cit. Newman and Abramson (1).

of the abstinence state seen so frequently in the alcohol addict upon withdrawal.

The Clinical Picture

Alcohol withdrawal, appearing 8 to 12 hr. after the last intake, is characterized by the appearance of psychomotor agitation which, if untreated, may progress to hallucinosis and finally to delirium and may be complicated by grand mal seizures (5). Associated symptoms and signs include a peculiar type of internal abdominal quivering usually confined to the epigastrium (and referred to by patients as "butterflies"); muscle cramps which primarily affect those muscle groups involved in locomotion; nausea; vomiting; insomnia; variable degrees of sweating; tachycardia; and diastolic hypertension. The following case, falling into the diagnostic gray area between the tremulous state and acute hallucinosis, demonstrates much of the symptomatology seen in both syndromes.

Case History

A 41-year-old white divorced male bank officer began tippling beer on 4 July 1960. Generally, he would drink 6 12-oz. cans of beer at his apartment after finishing work and before eating supper, occasionally as much as 10 cans. His appetite remained normal and he gained weight. The only untoward symptoms were slight mental fuzziness in the mornings on arising and, by August, a mushy stool usually passed immediately after rising. The latter often provoked anal itching and burning.

The patient's first drink of hard liquor during this bout was "a double vodka" at about 6 P.M. on 7 October (Figure 1). Later that evening he drank more beer. It was at this time that he began drinking in bars. He continued to drink beer every day and from 10 October on he increased his intake to 15 or 20 beers each night. By 14 October he was noting considerable tremulousness and a significant decrease in appetite. His food intake from this point on never exceeded the equivalent of one meal per day and on several occasions he did not eat at all. On the night of 15 October he returned to vodka, consuming half a pint. On 16 October he drank 15 to 20 beers and was essentially "blacked out" all that day. On 17 October he again drank vodka and continued to do so until the last 2 days of his binge, consuming as much as a fifth (of a gallon) each day.

Since he had been hired by the bank with the knowledge that he had a drinking problem, he felt obliged to phone the bank manager and admit that he was drinking. At this time he was extremely shaky. On 20 October he decided to "snap out of it." A girl friend in the same apartment building cooked a meal for him and he ate it. He drank no vodka this time but, instead, attempted to control his shakiness with 6 cans

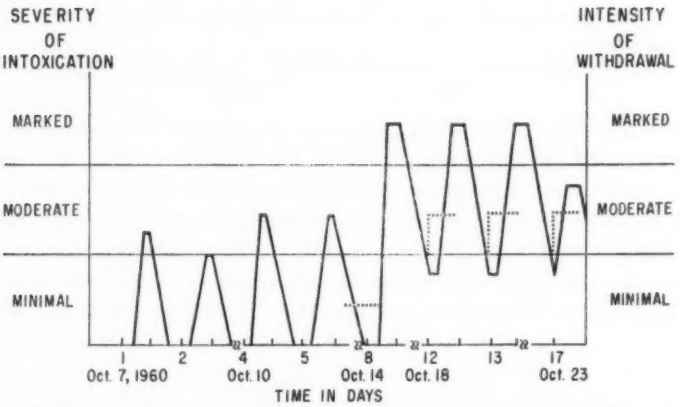

FIGURE 1.—*Duration and Severity of Intoxication and Withdrawal Symptoms during a Drinking Episode in an Alcoholic Patient.* Solid lines: intoxication. Dotted lines: withdrawal symptoms. Levels are estimates based on the patient's history.

of beer spread throughout the day. At 7 A.M. on 21 October he took 2 "single shots" of vodka to calm himself, then shaved and went to work, chewing gum to mask the odor of alcohol. By 10 A.M. he was so tremulous that he could no longer stand it and went to a bar for a double vodka. At noon he had another double vodka and finally he persuaded the manager to let him return home. He then finished off the afternoon with a series of double vodkas and "screwdrivers." Returning to his apartment he got a cab driver to bring him another fifth of vodka. By noon of Saturday, 22 October, he had finished the bottle and his funds were nearly exhausted. He therefore bought half a gallon of Tokay wine and finished almost all of it by that evening. On Sunday he awakened at 10 or 11 A.M. and began tapering off on beer, finally taking his last one at 11 A.M. the following day.

At 2:30 P.M. on 24 October the patient was seen by the nurse at the Alcoholic Rehabilitation Clinic. He was moderately agitated, although he was sweating only lightly, and hand tremor was minimal. The diarrhea which had been severe over the weekend was now subsiding. However, he had had dry heaves that morning and was experiencing definite hyperacusis. As he put it, "The exhaust of a car is like a Diesel engine." Hoarseness of voice was noted. Inadvertently, the initial blood pressure and pulse were not recorded. The patient was started at once on a regimen of oral chlordiazepoxide,[3] antacids and vitamins.

Withdrawal phenomena that were checked every day are shown in Chart I. The designations of general agitation as "marked" and of

[3] Librium, Hoffmann–La Roche, Inc.

CHART I.—*Withdrawal Phenomena Investigated Daily in an Alcoholic Outpatient*

	Positive	Negative
I. GASTROINTESTINAL		
Food Intake Diminished	x	
Nausea	x	
"Dry Heaves"	x	
Vomiting	x	
Diarrhea	x	
II. PSYCHIC AGITATION		
Agitation - General:		
Minimal		
Moderate		
Marked	x	
Quivering - Subjective Internal of:		
Epigastrium		0
Trunk and/or Extremities	x	
Insomnia	x	
Hallucinations:		
Auditory		0
Visual	x(?)	
Tactile		0
Delusions		0
III. MOTOR AGITATION		
Tremor of:		
Hands		
Minimal	x	
Moderate		
Marked		
Other Regions		0
III. MOTOR AGITATION (continued)		
Muscle Tenderness:		
Subjective	x	
Objective		?
Muscle Twitching		0
Muscle Cramps:		
Feet		0
Hands		0
Calves		0
Etc.		0
IV. NEUROLOGICAL AND SPECIAL SENSE DISTURBANCES		
Visual Disturbance	x	
Hyperacusis	x	
Paresthesias:		
Numbness		0
Tingling		0
Seizures		0
V. CARDIOVASCULAR AND MISCELLANEOUS DISTURBANCES		
Headache		0
Sweating:		
Day	x	
Night	x	
Blood Pressure:		
Systolic Elevation	x	
Diastolic Elevation	x	
Pulse Rate Elevation	x	

hand tremor as "minimal" indicate the greatest severity of these signs encountered during the period of observation. Because a portion of the hallucinosis may have been illusory (distortion of an existing object), a question mark was placed in the "positive" column. Figure 2 gives a roughly quantitative daily estimate of the intensity of withdrawal symptoms, based on the daily check of symptoms and signs shown in Chart I. Arbitrary weights were given to these and the resulting sums recorded.[4] In order to give an appropriate slope to the curve, the blood pressure and pulse values of the second day were used also for the first.

The patient returned to the clinic on 25 October stating that he had slept poorly. During the early morning hours he had had some transient but unusual visual experiences although he had remained oriented, i.e., the overhead light fixture looked like a bush and he had briefly seen the image of a face on the wall. He was now severely agitated and was sweating more heavily, although tremor remained minimal.

[4] The method will be described in another communication: JOHNSON, R. B. and HERBOLDT, V. M. A thirty-case study of some alcohol withdrawal phenomena. [To be published.]

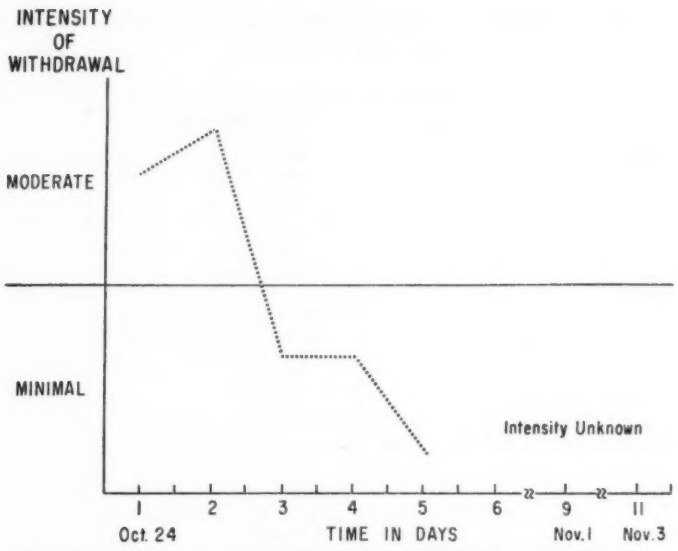

FIGURE 2.—*Duration and Severity of Withdrawal Symptoms after Cessation of a 17-Day Drinking Episode in an Alcoholic Outpatient.*

The blood pressure, with the patient seated, was 170 mm. Hg systolic and 110 diastolic, and the pulse was regular at 112 beats per minute.

The nurse saw the patient again on 26 and 27 October. On 28 October he was seen by the physician. He was considerably improved and accordingly all medication was stopped. The blood pressure was 124/78 and the pulse was regular at 92. He had been sleeping well on medication and had been eating a normal amount of food as on the preceding day. The sweating and hyperacusis had entirely subsided. Improvement was noted to have coincided with the diminishing dosage schedule of chlordiazepoxide.

The patient retained an increased startle reaction through 1 November and continued to sleep restlessly through the night of 3 November. Counting 24 October as day 1, the patient's total period of withdrawal was 11 days. The final diagnosis was acute hallucinosis.

It is both interesting and relevant to note that alcohol withdrawal does not begin following the last intake on the last day of drinking. Instead, the subject may experience withdrawal phenomena as early as the first or second day of a binge. Usually symptoms begin during the night while the individual is asleep and his blood alcohol concentration is falling. Although these withdrawal symptoms are usually mild, hallucinations and even seizures occasionally occur,

the various phenomena disappearing as further drinking reestablishes a sufficient blood alcohol level to suppress them. On termination of the binge the full-blown picture ensues, varying in severity according to the duration and intensity of drinking (5, 6), and the presence of dehydration, electrolyte abnormalities (7) or coincidental organic disease (6).

Under treatment with descending doses of alcohol, hypnotics or tranquilizers, singly or in combination, the tremulous and acute hallucinatory states reach their maximum intensity within 24 to 48 hr. By the end of 72 hr., significant improvement has occurred. This is followed by a rather long interval of less severe symptoms, the total period of withdrawal occupying perhaps 7 to 10 days. Delirium tremens somewhat alters the picture, since it often does not occur until 3 or 4 days after the last intake (6). Whichever state ensues is frequently followed by a period of overeating which usually lasts for several days. This is apparently a response to the deficient food intake and the resultant negative nitrogen balance which so frequently occurs during the period of heavy alcohol intake and the first few days of withdrawal.

Classification

Since 1813, when the English physician Thomas Sutton gave delirium tremens its name,[5] a modest literature devoted to the alcohol withdrawal states has accumulated. Despite this there has been a good deal of confusion regarding them. Theories of etiology, classification and treatment have long been in a state of flux (8). As was pointed out by Isbell and his co-workers (5), until the 1950's it was generally accepted in the United States that delirium tremens was caused by factors other than withdrawal of alcohol. Those most responsible for placing the physiological state of alcohol withdrawal in proper perspective include Victor and Adams (6), in their clinical study and review of the subject in 1953; Isbell and his associates (5), by their work both on alcohol withdrawal and on the closely related opiate and barbiturate abstinence syndromes; and finally, the World Health Organization's Expert Committee on Alcohol (9) by the statement of their official position in 1955. As a result of these efforts it has been quite clearly estab-

[5] Sutton, T. Tracts on Delirium Tremens, on Peritonitis, and on Some Other Inflammatory Affections, and on the Gout. London; Thomas Underwood; 1813. Cited in: Classics of the Alcohol Literature. Quart. J. Stud. Alc. 2: 179–196, 1941.

lished that alcohol is a substance to which an individual may develop tolerance and the withdrawal of which provokes a characteristic and highly stereotyped train of abstinence symptoms. Suppression of withdrawal symptoms may be accomplished by reintoxication with a variety of substances including alcohol itself, alcohol derivatives (e.g., chloral hydrate and paraldehyde), barbiturates and tranquilizers. In the light of former medical uncertainty, it is interesting to reflect on the alcoholic who, quite unaware of the controversy surrounding him, has for years empirically and often successfully treated his own withdrawal symptoms with tapered doses of alcohol.

Seven years ago, when we first attempted to classify the alcohol withdrawal states according to the Standard Nomenclature of Diseases and Operations (10), it was a routinely frustrating procedure. The reason for this subsequently became clear. By 1956 we had recognized that a large proportion of our cases were in a category which did not exist in the nomenclature of that period; the code designations of the Nomenclature then included only acute hallucinosis and delirium tremens. A survey of all cases seen at our clinic in 1955 (11), totaling 499 patients, showed a frequency ratio for delirium tremens, acute hallucinosis and uncomplicated withdrawal of 1:35:130. The specific ratio is unimportant and, in any event, is slanted because the population consisted entirely of outpatients, among whom one would expect fewer serious cases. Nevertheless it is clear that there is an overwhelming preponderance of minimally severe cases. Although this is hardly surprising, since it is characteristic of most other disease processes, such a gross deficiency in classification suggests the need for a more accurate conception of the alcohol withdrawal states and of their relation to prior alcohol intoxication.

"Acute brain syndrome, alcohol intoxication," is the general term used in the Standard Nomenclature to designate the various responses of the human organism to intoxication and withdrawal (10). Chart II is a graphic attempt both to incorporate and to classify these phenomena and to show their sequential relationships. Although the diagnostic category "tremulous state," which is shown on the chart, is being used increasingly in clinical practice, it is not yet officially accepted and does not have a code designation. A normal or pharmacological reaction is presumed to result from the combination of an essentially normal personality and the pro-

CHART II.—*Classification of States of Alcohol Intoxication and Withdrawal*

ACUTE BRAIN SYNDROME,
ALCOHOL INTOXICATION

INTOXICATION →	WITHDRAWAL
Behavior may be:	
1. Pharmacologic	Tremulous state
2. Abnormal:	Acute hallucinosis
a. With psychotic reaction	Delirium tremens
b. With behavioral reaction	
c. With neurotic reaction	

gressively depressant effect of alcohol. However, if there are significant personality aberrations, these frequently will be expressed as abnormal behavior which can be classified as shown. An individual who, while drunk, floridly displays abnormal behavior can frequently be shown to have significant conflicts in the personality area concerned. A common example is the person with a marked degree of poorly controlled hostility who acts out violently on minimal provocation when intoxicated. Psychotic reactions are more difficult to assess since bizarre behavior may occur during both dissociative and "blackout" periods. Whatever the behavior during intoxication, subsequent withdrawal symptoms will develop only if the individual has developed physical dependence, i.e., alcohol addiction. In turn the intensity of withdrawal will vary according to the duration of drinking, the amount of alcohol intake—seemingly irrespective of the beverage—per unit time, and other factors already noted.

Figure 3 illustrates the relative severity of various withdrawal states. The diagonally ascending hypotenuse of the triangle represents a continuum beginning with the least and terminating with the most severe withdrawal symptomatology. The vertical lines trisecting it represent superimposed arbitrary divisions designed to classify and organize withdrawal according to severity. The basis of all three withdrawal states is psychomotor agitation which in its simple uncomplicated form is termed the tremulous state. When true hallucinations appear, it is termed acute hallucinosis and, when disorientation supervenes, delirium tremens. Of course, diagnostic gray areas exist at the transition points between these categories.

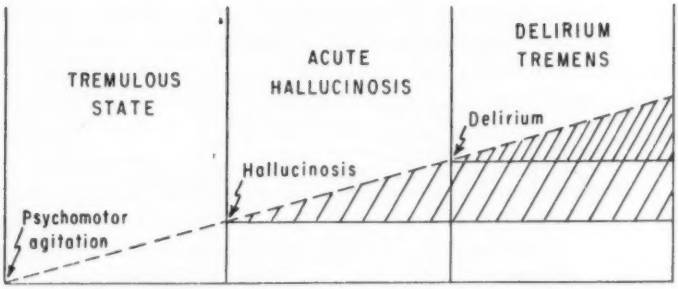

FIGURE 3.—*The Progressive Phases of Alcohol Withdrawal.* Axis measures severity of symptoms. Clear areas: psychomotor agitation. Wide stripes: hallucinosis. Narrow stripes: delirium.

Thus, it will occasionally be difficult to differentiate illusions from hallucinations. Where this is in doubt, acute hallucinosis should probably be the diagnosis.

DISCUSSION

Much remains to be done both to sharpen the clinical picture of alcohol withdrawal and to investigate the neurophysiological mechanisms involved. Nevertheless, a good deal of factual data are already available to the clinician. For example, experience indicates that no matter what sedative medication is used to suppress withdrawal symptoms, it should not be given on an "as required" basis. Instead, a dosage schedule of every 4 to 6 hr. should be prescribed, since the patient will "escape" from the effect of medication if longer intervals are allowed. Again, a history of prior seizures allows the prevention of their recurrence through the prophylactic use of anticonvulsant therapy. Further, the knowledge that delirium tremens has a latent period of up to 3 or 4 days may give the physician time to treat the preceding tremulous or acute hallucinatory state and prevent more serious withdrawal symptoms. In addition, because of the close relationship between duration and amount of drinking and the ultimate intensity of withdrawal, the resulting severity can be anticipated to some extent. The schedule in Chart III has been used as a crude guide at our clinic, but considerable overlapping in amount and duration occurs in actual practice. The schedule is based on the consumption of whisky but equivalent amounts of alcohol from other sources produce essentially the same end results. Of course, this is not quantitatively

CHART III.—*Relation of Amount of Whisky Consumed and Duration of Drinking to the Severity of Ultimate Withdrawal*

Amount per Day	Duration in Days	Resulting Withdrawal
1 pint	2 to 10	Tremulous State
1 pint	11 to 21	Acute Hallucinosis
1 pint	22 or more	Delirium Tremens
1 fifth	2 to 3	Tremulous State
1 fifth	4 to 7	Acute Hallucinosis
1 fifth	10 or more	Delirium Tremens

infallible, for it is the result of clinical impressions rather than of exact study. Furthermore, fever and fluid and electrolyte abnormalities caused by coexisting organic disease will increase the severity of withdrawal. Finally, precision in categorizing the withdrawal states is useful since it gives an opportunity for sound decisions regarding treatment and its most appropriate place. In most cases the tremulous state can be treated on an outpatient basis, provided one can be sure there will be no further drinking. However, the patient in acute hallucinosis usually requires hospitalization, and the one in delirium tremens, always.

SUMMARY

A brief review of neurophysiological data concerning alcohol withdrawal states has been presented. A case of acute hallucinosis has been reported with quantitative estimates of the intensity of the withdrawal syndrome. The clinical picture of all three withdrawal states has been described and a deficiency in their nomenclature has been cited. The quantitative and sequential relationships of intoxication and withdrawal have been emphasized and a diagrammatic concept has been presented for classification of withdrawal according to severity. Finally, some suggestions have been given for appropriate clinical use of existing knowledge.

REFERENCES

1. NEWMAN, H. and ABRAMSON, M. Relation of alcohol concentration to intoxication. Proc. Soc. exp. Biol., N.Y. 48: 509–513, 1941.
2. MIRSKY, I. A., PIKER, P., ROSENBAUM, M. and LEDERER, H. "Adaptation" of the central nervous system to varying concentrations of alcohol in the blood. Quart. J. Stud. Alc. 2: 35–45, 1941.

3. MELLANBY, E. Alcohol: Its Absorption into and Disappearance from the Blood under Different Conditions. (Great Britain, Medical Research Council, Special Report Series No. 31.) 48 pp. London; H. M. Stationery Office; 1919.
4. MCQUARRIE, D. G. and FINGL, E. Effects of single doses and chronic administration of ethanol on experimental seizures in mice. J. Pharmacol. **124**: 264–271, 1958.
5. ISBELL, H., FRASER, H. F., WIKLER, A., BELLEVILLE, R. E. and EISENMAN, A. J. An experimental study of the etiology of "rum fits" and delirium tremens. Quart. J. Stud. Alc. **16**: 1–33, 1955.
6. VICTOR, M. and ADAMS, R. D. The effect of alcohol on the nervous system. In: MERRITT, H. H. and HARE, C. C., eds. Metabolic and Toxic Diseases of the Nervous System; ch. 28. Baltimore; Williams & Wilkins; 1953.
7. SUTER, C. and KLINGMAN, W. O. Neurological manifestations of magnesium depletion states. Neurology **5**: 691–699, 1955.
8. BOWMAN, K. M. and JELLINEK, E. M. Alcoholic mental disorders. Quart. J. Stud. Alc. **2**: 312–390, 1941.
9. Alcohol and Alcoholism. Report of an Expert Committee. World Hlth Org. techn. Rep. Ser., No. 94, 1955.
10. PLUNKETT, R. J. and HAYDEN, A. C. eds. Standard Nomenclature of Diseases and Operations; 4th ed. New York; McGraw-Hill; 1952.
11. JOHNSON, R. B. 1955 Case Study of the Alcoholic Rehabilitation Clinic. Salem, Oreg.; Oregon Department of Finance and Administration; 1957.

A Controlled Study of Alcohol Withdrawal[1]

J. E. Rosenfeld, M.D.[2] and D. H. Bizzoco, M.D.[3]

ONCE a safe, simple and effective method of treating the acute manifestations of intoxication is developed, it may be expected that the medical profession will become wholeheartedly committed to the long-term treatment of the alcoholic. This would include his deviant emotional or mental make-up, any physical or physiological pathology, and his functioning in remission, when he reports limited alcohol intake, or "one or two drinks" or no drinking at all. An effective medical procedure for acute intoxication might also encourage wide general acceptance of these patients in hospitals. Physicians would consequently be less threatened through involvement with alcoholics and be prepared to treat them initially in their homes when indicated. Drugs are being developed in laboratories to serve this objective and are continually being tested, when safe, in hospitals, outpatient clinics and physicians' offices.

The present report is concerned with a study of the use of chlordiazepoxide[4] in the treatment of alcohol withdrawal, carried out at Blue Hills Hospital in patients admitted between May and October 1960. As a result of this study, chlordiazepoxide has become the basic drug used by this hospital for the treatment of all problem drinkers in uncomplicated states of alcohol withdrawal except for senile patients, who react with ataxia and confusion. Over 1,000 male and female patients have been treated in this hospital setting geared entirely to the treatment of alcoholics. Usually the patients arrive in intoxicated states, often having had their last drinks just before entering the building. Prior to the study of

[1] This study was carried out at Blue Hills Hospital, the inpatient facility of the Alcoholism Division, Connecticut State Department of Mental Health, Hartford.

Prominent roles in the planning and evaluation of the project were played by Leon A. Greenberg, Ph.D. and David Lester, Ph.D., both of the Laboratory of Applied Biodynamics and Center of Alcohol Studies, Yale University.

[2] Psychiatrist-in-Charge, Blue Hills Hospital.

[3] Senior Physician, Blue Hills Hospital.

[4] Librium, Hoffmann–La Roche, Inc.

chlordiazepoxide, many other drugs and approaches were used. The most reliable drugs were insulin, paraldehyde, chloral hydrate and the barbiturates, especially in delirium tremens, acute hallucinosis and marked dehydration. After the opening of the hospital in 1949 the medical treatment program included these previously accepted and proven drugs, intravenous infusions, restraint of overactive, delirious and hallucinating patients, and so on. After the introduction of chemotherapy for alcoholics, habit-forming drugs were used less often. Intravenous fluids, with or without drugs, were employed. Although chemotherapy is now recognized as of the greatest importance in the treatment of alcoholism, paraldehyde continues to be recommended by many as the drug of choice in the treatment of acutely intoxicated patients.[5] Beginning 4 years ago, the former classic drugs were used less and less frequently at the hospital and since 1959 they have not been used at all. Six new substances were tested in various studies, most of which were double-blind, and those found effective were included in the program. Thus the earlier drugs began to be prescribed only for unresponsive patients.

Preliminary Study

The present study began by testing chlordiazepoxide in 25 patients. Since the drug used was known to the staff, several questions were raised about it, e.g., dosage was reported to be an individual and frequently difficult problem and there were references to increased rate of alcohol metabolism.

Procedure

The dosage first used was 50 mg. intravenously on admission, repeated if necessary after 3 hours and again after 6 hr. The drug was then given by mouth in gradually diminishing doses until a maintenance dose was established. At this dose level many patients did not go to sleep, most others awoke after 30 to 60 min. and demanded more of the same medication. This request for the same drug was most significant. Since this schedule was found insufficient, the initial dose in the fifteenth patient was increased to 75 mg. and in the eighteenth patient to 100 mg. At this level patients routinely fell asleep for 2 or 3 hr., could be aroused to take liquids if necessary, awoke refreshed with good appetite, and expressed surprising comfort. Extra medication was very rarely requested and other drugs, not at all. The total dose

[5] Arieti, S., Ed. American Handbook of Psychiatry. New York; Basic Books; 1959.

was kept at 150 mg. for the first 24 hr. After that time patients were ready to participate in the hospital program.

Results

All patients were tested for blood alcohol by means of the Alcometer on admission. The first nine patients were tested a second time 1 hr. after medication, and a third time 1 hr. later. There were no differences in the findings between these readings and those when meprobamate or various phenothiazines were used. Most of the patients showed a rise of 0.02 per cent 1 hr. after admission and then a gradual fall. This indicated that there was no apparent change in the metabolism of alcohol.

Icteric index studies were performed in the 25 patients in the chlordiazepoxide group and in more than 35 patients receiving other medication who served as controls. There were no apparent differences.

Four cases of ankle edema were discovered among the chlordiazepoxide-treated patients 24 hr. or more after beginning medication. The first 3 were taken off chlordiazepoxide and the edema subsided, the fourth patient was kept on the drug and given Diuril. This proved effective.

Vomiting occurred in 2 of the first 14 patients. It was controlled in 1 by a single dose of chlorpromazine. The other patient was taken off the drug.

After the large initial doses, patients often showed drowsiness, and grogginess up to ataxia was observed in two. On maintenance doses this symptom was not present.

Double-Blind Study

Procedure

After this initial test a double-blind study using chlordiazepoxide and placebos was set up. The code was not seen by any hospital staff member, including the principal investigators, until the project was completed. The standard hospital rating sheet for research studies on drugs was used. Each patient under 65 was given medication in the order of admission from numbered packets, whose order was determined by a table of random numbers. Each packet contained a complete 5-day supply of project material (either drug or placebo) including a bottle of 50 capsules, each containing 10 mg. of project material; 2 vials, containing 10 mg. of project material each; and 2 vials containing 1 ml. of sterile diluent each.

Each patient received an initial dose of 100 mg. of project material intravenously. If indicated, this dose could be repeated 1 hr. later and again an hour after that. The project material could be discontinued 1 hr. after the initial injection at the discretion of the physician if the patient exhibited psychotic symptoms or was too ill to be denied a known drug. A shift could also be made 30 min. after the second dose. The treatment code and the results in each patient are given in Table 1.

Following the initial parenteral medication, the patients were given capsules totaling 50 mg. or less as indicated until effective results were achieved. As the symptoms and signs of intoxication, hangover or delusions subsided, the patients were given diminishing doses until the packet was used up. The study continued for 5 days in each patient who remained in the hospital that long. Thereafter, the patient was maintained with 20 to 80 mg. of chlordiazepoxide a day in divided doses if there was a complete absence of side effects and the patient requested the capsules.

Results

It can be clearly seen from the results given in Figure 1 that patients who received the drug changed and those who received the

TABLE 1.—*Results of Treatment in 30 Subjects Given Chlordiazepoxide and 30 Controls Given Placebo*

Patient No. & Sex	Treatment*	Result†	Patient No. & Sex	Treatment	Result	Patient No. & Sex	Treatment	Result
1 m	P	0	21 m	D	3	41 m	P	0
2 m	P	2	22 m	D	3	42 m	D	2
3 m	D	3	23 f	P	0	43 m	P	0
4 m	D	3	24 m	D	3	44 m	D	0
5 m	P	1	25 m	P	0	45 m	P	2
6 m	D	3	26 m	D	3	46 m	D	3
7 m	D	0	27 m	P	0	47 m	P	0
8 m	P	2	28 m	P	0	48 m	P	0
9 m	P	3	29 m	D	3	49 m	D	2
10 m	P	3	30 f	P	0	50 m	D	2
11 f	D	0	31 m	D	3	51 m	P	0
12 m	D	0	32 m	P	2	52 m	D	3
13 m	P	0	33 m	D	3	53 m	P	3
14 m	D	3	34 m	D	0	54 m	P	0
15 m	P	0	35 m	D	1	55 m	P	0
16 m	D	2	36 f	P	0	56 f	D	3
17 m	D	3	37 f	P	1	57 f	D	3
18 m	P	0	38 m	D	0	58 m	P	0
19 m	D	2	39 m	D	0	59 m	P	2
20 m	P	0	40 m	P	0	60 m	D	3

* P = placebo; D = drug.

† 0 = unimproved. 1 = slight improvement. 2 = moderate improvement. 3 = marked improvement.

placebo did not change in any significant degree. Combining the two lefthand and the two righthand categories in the figure shows that after 5 days of hospitalization 22 of the subjects but only 8 controls could be considered well. Application of Fisher's test to a 2 by 2 table based either on the above combination or on a comparison of the markedly improved and unchanged patients yields $P<.001$. The effect of chlordiazepoxide, thus, was highly significant.

Of the 60 patients, 4 developed delirium tremens and 2, acute hallucinosis. Only 1 patient, in delirium tremens after the first dose, required a second intravenous dose of 100 mg. On decoding, it was found that he had received chlordiazepoxide. Another delirium tremens patient, who also received the drug, responded sufficiently to leave against medical advice on the second day. He was the only patient to require occasional restraint for periods of about 1 hr. during the first 12 hr. of hospitalization. Two patients given placebos developed delirium tremens. One was shifted to chlordiazepoxide and the other to a phenothiazine, and both responded well.

The two cases of acute hallucinosis were both receiving the drug, as ultimately revealed. One responded well; the other was shifted to a phenothiazine and was adequately controlled.

Alcometer readings on admission showed the following blood alcohol levels (in per cent) in subjects and controls, respectively: 0: 8 and 8; >0–0.10: 12 and 14; 0.11–0.20: 8 and 6; 0.20 or over: 2 and 2. The similarity in numbers of patients from each group at the various levels occurred by chance.

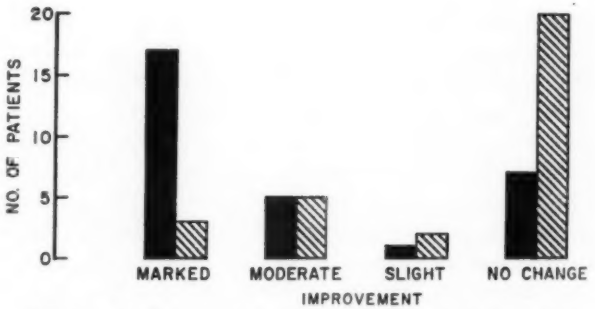

FIGURE 1.—*Degree of Improvement in Subjects Given Chlordiazepoxide and in Controls Given Placebos During a 5-Day Period of Hospitalization.* Black bars: subjects. Striped bars: controls.

Since Blue Hills Hospital is an open institution, patients are released on request when not dangerous to themselves or others. The length of hospital stay by drug-treated and placebo-treated patients, respectively, was as follows: 1–5 days, 7 and 1; 6–10 days, 11 and 0; 11–15 days, 8 and 19; and 16 days or more, 4 and 10. The longer stay of placebo-treated patients is understandable since most of them did not receive drug therapy until the sixth day of hospitalization. The controls also waited longer than the subjects before raising the question of discharge. Five patients who left against medical advice and 1 who absconded were all receiving chlordiazepoxide. This indirectly indicates the patients' improvement and consequent omnipotent thinking. The only patient receiving placebo who stayed for only 3 days left with medical approval.

Aside from therapeutic doses of vitamins, the only other drug used frequently was Doriden in doses of 0.5 g., for sleep. There was no striking difference between drug and placebo patients in the number and frequency of requests for sleep medication. Dilantin was given when required to control convulsions.

Of the 30 patients who received chlordiazepoxide, 26 remained long enough for weight checks and they showed an average gain of 9 pounds; only 2 merely maintained their weight. The placebo-treated patients all gained weight, the average being 8.5 pounds. Although of itself not significant, the longer stay of placebo patients does alter the relation considerably.

There were no complications from the drug. At high dosage, almost all patients complained of drowsiness or weakness. This disappeared with adequate reduction in drug and is of no serious consequence. In cases of interference with walking, patients were kept in bed until lowered doses reduced the disturbance. Only one placebo-treated patient complained of drowsiness.

Ankle edema occurred in four patients who received chlordiazepoxide but this did not necessitate cessation of treatment. Diuril reduced the swelling but it disappeared only after a few days on the lowest doses of chlordiazepoxide. The pathology involved in this disturbed water balance is not yet determined. Elevation of the lower extremities, limited walking and absolute bed rest had no noticeable effect on the swelling. In the course of the year we continued to observe such edema in about 5 per cent of patients treated with chlordiazepoxide. It became manifest to patient or

physician during the first few days after the patient received large initial doses. The dose is now quickly reduced and this suffices to produce detumescence.

Since the completion of the project, patients have been treated with oral chlordiazepoxide whenever they can cooperate; otherwise, the intramuscular route is used since it is almost as rapid in effect and less dangerous and troublesome than the intravenous. When the drug is given orally, it takes about 15 to 20 min. longer for the patient to fall asleep at high dosage or to show visible effect from smaller quantities.

Under this regimen, no other drugs were required to produce manageable, fairly quiet and cooperative patients. Some patients remain somewhat anxious and restless for a time. All tolerate their condition and none is disruptive. They readily talk to personnel or family in lucid fashion. It appears, therefore, that chlordiazepoxide can be used in the general hospital to produce quiet and cooperative alcoholic patients. It does not seem to shorten the period of delusions and hallucinations, but it calms the patient markedly, diminishes anxiety and restlessness, enormously minimizes the need for restraints and deep sedation, and virtually eliminates the need for routine intravenous fluids in psychotic episodes.

Treatment can be initiated in the patient's home in states of intoxication or hangover and continued there so long as delirium or hallucinosis does not develop.

Summary

Studies on the effect of chlordiazepoxide in alcohol withdrawal states, carried out at Blue Hills Hospital, an inpatient facility for alcoholics, are reported. A preliminary study involving 25 patients was used to test various dose levels and to observe side effects. No differences were found in rate of alcohol metabolism or in icteric index between patients receiving chlordiazepoxide and those given other medication. Ankle edema occurring in some chlordiazepoxide-treated patients could be reduced by diuretics and eliminated by lowering chlordiazepoxide dosage. Drowsiness and weakness following high dosages disappeared when the dosage was reduced.

In a double-blind study of 30 subjects receiving chlordiazepoxide and 30 controls given placebos, the initial dose was 100 mg. ad-

ministered intravenously, repeated if necessary 1 hour later and again 1 hr. after that. This was followed by 20 to 50 mg. in capsules administered orally as indicated until effective results were achieved. The study lasted for 5 days in each patient. Patients could be switched to a known drug at the discretion of the physician. Marked or moderate improvement was seen in 22 subjects and 8 controls in 5 days. The rest showed only slight improvement or none. This difference between subjects and controls was highly significant ($P<.001$). Placebo-treated patients also stayed in the hospital much longer than did the subjects. The effects of chlordiazepoxide on delirium tremens, acute hallucinosis, sleep and weight are described and side effects and methods of administration are discussed.

Treatment of Alcoholism in a General Hospital

John D. Schultz, M.D.[1]

THE TREATMENT of acute alcoholic states on the wards of the general hospital is receiving increasing emphasis (1–5). There is no longer any need for the heavy odor of paraldehyde permeating the entire nursing unit and beyond. It can now be stated categorically that this drug should never be used. It is dangerously toxic in amounts sufficient to control severe degrees of hyperactivity and it is addicting. Management need no longer be complicated by the use of restraints nor is it necessary to use the "strong room" for disturbed behavior. Most important, it is now recognized that long-term treatment of alcohol addiction should be initiated along with the medical management of the acute toxic state, and both aspects must be approached vigorously to achieve any significant degree of success. Such a total program has been developed at the District of Columbia General Hospital in Washington, a large municipal hospital of 1,250 beds. The principles underlying this approach are applicable to any general hospital.

About 2,000 alcoholics are admitted to this hospital each year. This number has risen slowly over the past 10 years but is fairly predictable. It represents about 6 per cent of the estimated 30,000 alcoholics in the District. By and large only "emergency cases" are admitted. Uncomplicated drunkenness is not regarded as an emergency. Thus the alcoholic patient population is very sick, probably much more so than the average admission to the private general hospital. In essence, the techniques developed to meet the needs of the more critically sick patients are applicable also to the milder toxic states.

The data in the present report were derived from three sources. An analysis of the admissions during the year 1960 was made to

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determine the diagnostic categories, types of complications and range of treatments used. Statistics were examined on all alcoholic admissions in the past 5 years, during which period rather elaborate data were recorded. Finally, a detailed study was made of 100 patients selected at random from admissions during the 4-month period January–April 1961. This latter group, involved in a long-range controlled drug study which will be reported in detail elsewhere, consisted of 28 with the diagnosis of acute brain syndrome, 57 with delirium tremens, and 12 with acute alcoholic hallucinosis. Three patients who were transferred to other wards were excluded from this count. The average time in the hospital for these 3 categories of patients was 5.2, 7.4 and 8.8 days, respectively.

Acute brain syndrome was used to describe those toxic states involving confusion, clouding of the sensorium and agitation but without demonstrable auditory or visual hallucinations. Delirium tremens cases included, in addition to this symptom complex, manifest hallucinations, which were predominantly visual. Acute hallucinosis differed in that there were both delusions and hallucinations, the latter often auditory, and a relatively clear sensorium. This dividing line is arbitrary and it does not seem that the difference between delirium tremens and acute hallucinosis represents any significant difference in etiology. There are, however, underlying differences in the psychodynamics which determine the nature of the content disturbance.

As there were no cases of simple intoxication in this special study group, the relatively short duration of stay is noteworthy. The acute toxic state was often relieved in 24 hours and the average duration of the acute state was approximately half the total length of stay. The acute toxic state was considered to have been resolved when temperature was normal, the patient was freely taking nourishment and fluids in the dining room, the sensorium was clear, and there were no longer hallucinations or delusions. Some tremulousness often persisted to the time of discharge.

The Treatment Setting

Since alcoholism must be treated in both its acute and long-range aspects, it has been found advantageous to set up a special treatment area for this illness. This is not necessitated by disturbed or intractable behavior, which can be adequately controlled with

drugs, nor is there any thought of isolating the alcoholic from other patients. The reasons are positive and include the following:

1. Even in small groups the alcoholic gains a sense of security, relieved of the feeling of being different, cast out and alone. A day room is provided where during recovery the alcoholic can socialize with others who have the same problem. Alcoholics Anonymous meetings and group therapy meetings are held here. Ward rounds and interviews are conducted openly in this area.

2. The alcoholic treated in this atmosphere feels that he is in the hands of therapists especially skilled in the management of his problem. This makes it easier to establish early rapport, which is essential to overcome the alcoholic's skepticism concerning any treatment and to lay the foundation for rehabilitation.

3. Such a unit can be part of a general medical service, or part of the psychiatric facility, as in the present case, yet be sufficiently identified as a separate area so as to avoid the alcoholic's reluctance to associate his problem with anything "mental." Initially, in most cases, acceptance of the idea that his problem has anything to do with a neurosis is impossible for the alcoholic, because such a concept adds to the already unbearable feelings of inadequacy and inferiority which are basic factors in his use of alcohol for escape from anxiety.

4. A major advantage is the very substantial gain accruing from developed nursing skills. This is hard to define specifically, but is vital in many aspects, where signs of possible relapse, threatening convulsions, rate of early, safe ambulation, and other details of ward management require a subtlety of judgment gained only after long experience with this type of patient.

For convenience, management of the acute and the rehabilitative phases will be discussed separately although the importance of integrating these two aspects of treatment from the beginning cannot be emphasized too strongly.

Treatment of Acute States

In the acute phase it is immediately necessary to recognize the existence and the extent of complications. In our intensive study of 100 cases, the following complications were recognized: bronchi-

ectasis, pneumonia, asthma, emphysema, cystitis, prostatitis and syphilis. These entities indicate the range of serious problems. There were many minor secondary symptoms which required treatment. In addition, 8 patients exhibited at least one grand mal seizure. We have come to use the term "alkolepsy" for grand mal seizures seen in alcohol withdrawal states. Previous data from our service indicate that this incidence of approximately 8 per cent is low. Thirty-five of the patients gave a history of prior seizures. When such a history was obtained, or when the nature of the tremor was extreme, with clonic jerks suggesting impending seizures, Dilantin and phenobarbital were administered immediately upon admission. A standard regimen was intramuscular injection of 250 mg. of Dilantin initially and 100 mg. orally four times the first day together with 32 mg. of phenobarbital in elixir form four times. The dose of these medications was gradually diminished on the second and third day if the toxic state subsided rapidly.

Other complications which should be watched for, and may easily be missed unless the physician is alert, include: subarachnoid hemorrhage, fractures, including sinus fracture, atypical pneumonitis (including aspiration pneumonia), urinary tract infections, duodenal ulcer complications and pancreatitis.

Routine medication at this hospital now includes the following:

1. Intramuscular injection of 50 to 100 mg. of chlordiazepoxide,[2] repeated two to four times in the first 24 hours, the dose varying with the degree of hypermotor excitement. This is continued parenterally on the second day or longer if necessary and is followed by 50 mg. of chlordiazepoxide four times a day orally for 1 or 2 days. Some of the staff have preferred to give oral chlordiazepoxide from the beginning along with the parenterally administered drug, with the thought that this would maintain a more uniform level. However, this procedure would seem to have no real advantage. Whether administered parenterally or orally, the drug is slowly metabolized; it is continued until the immediate toxic state is resolved.

Our staff is free to choose the tranquilizer with which they are most familiar. Most of them now use chlordiazepoxide, although chlorpromazine,[3] promazine[4] and other phenothiazines have been and are still widely employed. We have published our experience

[2] Librium, Hoffmann–La Roche, Inc.
[3] Thorazine, Smith, Kline & French.
[4] Sparine, Wyeth.

with chlorpromazine (6), dimethylamino-*n*-propylphenothiazine (7) and trifluoperazine[5] (8). Chlordiazepoxide produces a more muscle relaxant effect than these other preparations, as well as less hypotension and less drowsiness (9); hence it is presently the drug of choice. There is a newer analogue which will be introduced in a controlled study soon to be initiated.

2. Chloral hydrate in doses of 1 to 2 g. is given as bedtime sedation. Chlordiazepoxide produces almost no hypnosis and sometimes even seems to stimulate wakefulness. Chloral hydrate with chlordiazepoxide provides restful sleep in nearly all instances.

3. Berocca-C-500, in a dose of 4 cc. each day for 4 days, is given parenterally.

4. Close observation and control of fluid intake are maintained. Fluids are pushed orally. With the advent of the tranquilizers it became quite feasible to use the oral route for hydration. Only 1 patient in the 100-case study required intravenous fluids.

Treatment of Alcoholism

Treatment of withdrawal alone, with no attention to the long-term aspects of alcoholism, would accomplish very little. A statistical study initiated several years ago revealed that less than 5 per cent are readmitted in any one year. The proportion increases to 15 per cent in 2 years and to nearly 75 per cent over a 15-year period.

Treatment emphasis from the beginning is on various modalities of milieu therapy. The importance of the nursing unit atmosphere has already been emphasized. Each patient is evaluated in terms of his individual needs. A team approach is utilized. Early ambulation is encouraged. Daily teaching rounds are made, attended by the nursing personnel. Ward management conferences are held each week. Recreational activities, including dances, motion pictures and athletic sports are planned for the evening and patients are encouraged to attend. Television and activities involving patient–personnel interactions are available for those who prefer to remain within the ward.

Most important, group interaction is encouraged in all phases of the program. Patients who have recovered sufficiently from

[5] Stelazine, Smith, Kline & French.

their physiological distress offer support and understanding companionship to those who have not yet reached this level.

As soon as the patient is accessible, efforts are made to plan long-range treatment after discharge. Considering the recognized difficulties that long-range treatment of alcoholism presents, our results are encouraging. A few patients go to the Out-Patient Alcohol Clinic, a very few into private psychotherapy. Many receive immediate assistance from Harbor Lights and other social agencies. A small number with Korsakoff's syndrome or other psychotic states are committed or admitted to Veterans Administration mental hospitals. A very small number who face drunkenness charges must go to the workhouse if they cannot pay the fine. Actually, this involves very few of our patients. Twenty thousand alcoholics are committed each year by the courts of the District of Columbia to Occoquan, the local workhouse. These are all cases of acute intoxication who sober up in jail and cannot pay a fine. This statistic is cited to emphasize again that the patients hospitalized at the District of Columbia General Hospital represent a substantially small but very sick group.

The most effective long-term results are provided by two resources: Alcoholics Anonymous and the hospital's Rehabilitation Program.

For about 10 years a liaison relationship has existed between the hospital and A.A. and this has gradually developed into an effective partnership. A member of A.A. is now employed as a nonprofessional member of the Alcoholic Service staff with primary responsibility for coordinating activities with A.A. With few exceptions, the only cases of acute intoxication admitted to the hospital are validated A.A. members who have "slipped." They are admitted directly, bypassing the admitting office, in order to facilitate rapid treatment for quick recovery and return to the A.A. program. Representatives of A.A. are on call 24 hours a day, 7 days a week, to serve the patients admitted. Three A.A. meetings are held each week at the hospital and a hospital group was recently formed. Although statistics are not available, the effectiveness of their program is obvious.

The other important resource, the Rehabilitation Program, is jointly operated by the Psychiatry Service and the Physical Medical Rehabilitation Service. Patients who express an interest and exhibit proper motivation are interviewed and presented to the rehabilita-

tion team. They are placed on a work therapy program conducted in the hospital and are followed by the work therapist. They are assigned to hospital industries or to various levels of management. These patients remain in hospital status until they have established themselves and gained the confidence they need to function in the community.

This program is soon to be greatly expanded. At a cost of nearly $1,000,000 old psychiatry buildings are being reconverted into a 180-bed half-way house. This will be a day–night care center, largely patient-operated, with a complex program.

With respect to job opportunities, about 30 ex-alcoholics are now regular employees of the hospital, with civil service status. In 5 years' experience only 2 of these have had any problem with alcohol. Most are in A.A.; a few came from our Rehabilitation Program.

Summary

The management of alcoholism at the District of Columbia General Hospital in Washington, D. C., is described. A total approach is emphasized, directed toward simultaneous treatment of both acute toxic effects of alcohol and long-term therapy for alcoholism. Reasons for setting aside a specific treatment area for this condition within the hospital are outlined.

Treatment of acute intoxication includes watching for complications and routine medication with a tranquilizer (usually chlordiazepoxide), chloral hydrate for bedtime sedation, vitamins and oral fluids.

Emphasis in the treatment of alcoholism in the hospital is on providing a therapeutic milieu through the setting and through a team approach with well-oriented personnel.

On discharge the most effective resources for patients have been Alcoholics Anonymous and the hospital's Rehabilitation Service. A half-way house connected with the hospital is currently being established.

REFERENCES

1. Hospitalization of patients with alcoholism. J. Amer. med. Ass. (Report of Officers.) 162: 750, 1956.
2. Berke, M., Gordon, J. D., Levy, R. I. and Perrow, C. B. Nonsegregated hospitalization of alcoholic patients in a general hospital. Hospitals 33 (No. 22): 45–48, 1959.
3. Berke, M. Care of the alcoholic in a general hospital. Sth. Hosp. 29 (No. 4): 27–30, 1961.

4. Sister Blandine. Care of alcoholics in a general hospital. Hosp. Mgmt 90 (No. 4): 6–7, 1960.
5. Brunner-Orne, M. The role of a general hospital in the treatment and rehabilitation of alcoholics. Quart. J. Stud. Alc. 19: 108–117, 1958.
6. Schultz, J. D., Rea, E. L., Fazekas, J. F. and Shea, J. G. Chlorpromazine in the management of acute alcoholic states. Quart. J. Stud. Alc. 16: 245–250, 1955.
7. Fazekas, J. F., Sullivan, P. D. and Schultz, J. D. Use of dimethylamino-n-propylphenothiazine in the management of patients with acute mental disturbances. Med. Ann. D.C. 25: 67–69, 1956.
8. Costa, J. S. and Hoffman, E. T. The use of trifluoperazine for acute alcoholism. Med. Ann. D.C. 29: 556–558, 1960.
9. Ticktin, H. E. and Schultz, J. D. Librium, a new quieting drug for hyperactive alcoholic and psychotic patients. Dis. nerv. Syst. 21 (Suppl. No. 3): 49–52, 1960.

Rehabilitation of the Alcoholic

Earl H. Mitchell, M.D.[1]

FOR CENTURIES the problems created by the excessive use of beverage alcohol have remained unsolved. Even at the present time the etiology of this disorder is unknown and the variety of treatments available suggests that none is consistently effective. As the great complexity of the problem has become more generally recognized within recent years and the therapeutic failure of the strict moralistic approach has been acknowledged, several notable changes have come about in the management and rehabilitation of the alcoholic.

The beginning was the founding of Alcoholics Anonymous in 1935. This fellowship numbers more than 250,000 recovered alcoholics, a remarkable achievement considering the former hopeless outlook. Stimulated by the success of Alcoholics Anonymous, both professional and lay groups have gradually accepted the premise that alcoholism is a behavioral disorder from which the alcoholic can recover more readily when given understanding, acceptance and love rather than punishment, condemnation and confinement.

While these changing attitudes were developing, the ataractics were introduced into medical practice. Their use in the acute post-intoxication phase has greatly simplified the task of the physician and eased the discomfort of alcohol withdrawal for the patient. The effectiveness of the ataractics has also made the alcoholic a much more acceptable patient than formerly, so that now he is often treated in a general hospital or a physician's office instead of under restraint in a sanitarium or mental hospital.

The physician who provides medical support and understanding counsel for the alcoholic may often succeed in bringing about lasting recovery but at other times there will be little or no improvement. The difficult patient is frustrating and bewildering and the poor results of his treatment are usually blamed upon his lack of cooperation, poor motivation or inadequacy. These factors may

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explain some failures, but every physician at times will ask, "Where did I fail? What could I have done differently? How could I have been more effective?"

The needs of this group of patients who do not respond well to treatment in the general hospital were responsible for the development of a rehabilitation facility for alcoholics near Washington, D. C.,[2] which had been in operation for 15 months at the time of this report. Three basic concepts underlie the program at this facility. First, the alcoholic needs time to recuperate from the toxic effect of alcohol upon the brain. Though most effects of intoxication disappear within a few days, some degree of impaired judgment and confused thinking may continue for several weeks after the last drink. A protected therapeutic environment was considered to be desirable during this time. Second, the alcoholic will recover more readily if given treatment in an environment designed for his special requirements. Care in a general hospital, though quite adequate for treatment of acute intoxication and its complications, seldom offers a planned rehabilitation program. The outpatient clinic may have such a program, yet be unable to deal effectively with the patient who cannot abstain from drinking or who is still recuperating from heavy alcohol intake. Third, the patient will learn about alcoholism and its symptomatology more readily and be stimulated to recovery more rapidly through group therapy with other alcoholics than in individual treatment or in a group with other types of emotional disorders.

Facilities and Staff

With these concepts in mind a 40-acre farm located between Washington and Baltimore was purchased and converted into a 14-bed hospital. Admission is restricted to voluntary patients who are not drinking and who have a primary diagnosis of alcoholism. The recommended treatment period is 4 weeks but patients may leave sooner if they wish to do so. Preadmission examination is performed by the referring or staff physician and patients who are intoxicated or acutely ill from drinking are referred to a general hospital for necessary preliminary treatment.

The staff consists of an administrator, a program director and counselor, two part-time physicians, a graduate nurse, and housekeeping employees. Special attention is given to the selection of

[2] Melwood Farm, Olney, Md.

the staff to insure that they will be a source of support and helpfulness rather than custodians. Three of the staff members are recovered alcoholics and their dedication and interest in the project have been invaluable.

The program is multidisciplinary, with attention given to the physical, emotional and spiritual needs of the patient. Clergymen in the village are frequent visitors and have helped many of the patients develop a better understanding of the role of a spiritual life in rehabilitation. Patients who have been members of a church are encouraged to renew this source of support.

Regular meetings of Alcoholics Anonymous are held at the farm once a week and association with these recovered alcoholics often creates friendships which continue after the patient returns to his home. Members of Alcoholics Anonymous participate in recreational and social activities as well as in informal group discussions.

The program gives the patient 2 hours of formal instruction each day. A series of lectures on alcoholism by the staff physicians have been very popular. The physicians also give individual counseling to both the patient and his family. Teaching films on alcoholism, tape recordings and selected reading assignments are also provided. Counseling and group therapy are informal and have been the most useful part of the program.

Sample and Procedure

As of May 1960, 180 patients had been admitted. The first 60 of these (33 men and 27 women) comprised the study group. The average duration of their hospitalization was 14 days. The control group was made up of 60 alcoholics who were treated medically in another hospital for an average of 4 days. They were admitted for treatment of intoxication and on discharge were asked to visit their own physician or the alcoholic clinic and to attend Alcoholics Anonymous. Patients in the study group were usually better motivated and demonstrated more insight when treatment began than those in the control group. The period of observation in both groups was 6 to 12 months after discharge.

Upon entering the hospital the alcoholic finds himself in a strange environment and he must begin to face many problems and conflicts without the solace of alcohol. The degree of stress and anxiety experienced during the first few days in the hospital is usually greater than while the patient is drinking. Symptomatic relief provided by ataractics during this period of readjustment helps to establish rapport with the physician and permits the patient to begin his rehabilitation sooner. Psychopharmacological agents most helpful in this readjustment are

chlordiazepoxide,[3] meprobamate,[4] promazine,[5] barbiturates, and amine oxidase inhibitors. Combinations of these drugs have often been more effective than their separate use.

In the study group, 42 patients (70 per cent) received 30 to 100 mg. of chlordiazepoxide; 17 patients (30 per cent) were given 600 mg. of meprobamate combined with 75 mg. of promazine orally in divided doses and 1 patient received no medication. The length of drug treatment was 2 to 23 days with an average duration of 9 days. Fifty-three patients (90 per cent) were given 100 mg. of pentobarbital at bedtime to help them sleep during the first 5 to 7 days after admission.

Results and Discussion

Chlordiazepoxide was found to be free of undesirable side effects and safely reduced stress and tension when used in these doses. There was no noticeable drowsiness or ataxia when the dose was 30 mg. per day or less. No patient in the study or control groups who received chlordiazepoxide developed physical dependence or habituation.

Patients without severe emotional disturbance were withdrawn from sedation and tranquilizers 5 to 7 days after their admission. Regular hours for rest and exercise, proper diet and a quiet, peaceful environment were found to be good substitutes for medications.

In order to determine the results of treatment in each group, a questionnaire (Chart I) was sent to each patient 12 months after discharge. Information collected in this way was supplemented by personal interviews. An arbitrary value was given to each answer on the questionnaire and each patient was accordingly classified as excellent, improved or unimproved. Comparative results of this classification in subjects and controls are given in Figure 1. Causes of death in the 6 deceased patients were: Laënnec's cirrhosis 1, fulminating pneumonia 1, suffocation 2, and myocardial infarction 2. Three of these patients had been drinking heavily just prior to their terminal illness and 3 were abstinent at the time of death.

The comparative rates of readmission in subjects and controls are given in Figure 2.

Contrary to expectations, the length of hospitalization did not appear to have much effect upon recovery in the study group. Some patients who were hospitalized for only a few days did well while

[3] Librium, Hoffmann–La Roche, Inc.
[4] Miltown, Wallace Laboratories.
[5] Sparine, Wyeth Laboratories.

CHART I.—*Follow-up Questionnaire Sent to Patients and Controls 12 Months After Discharge from Hospital*

1. HAVE YOU BEEN DRINKING?
   - ☐ MORE
   - ☐ LESS
   - ☐ SAME
   - ☐ NONE

2. HAS YOUR ATTENDANCE AND EFFICIENCY AT WORK BEEN
   - ☐ WORSE
   - ☐ IMPROVED
   - ☐ SAME
   - ☐ UNEMPLOYED

3. HAVE YOU ANY NEW INTERESTS?
   - ☐ NO
   - ☐ HOBBIES AND CRAFTS
   - ☐ FAMILY OR FRIENDS
   - ☐ BOOKS AND ART
   - ☐ RECREATION AND SPORTS
   - ☐ OTHER

4. HAVE YOU BEEN ABLE TO MANAGE YOUR PROBLEMS?
   - ☐ LESS WELL
   - ☐ BETTER
   - ☐ SAME
   - ☐ DON'T KNOW

5. HAVE YOU CONTINUED TO GET HELP FROM
   - ☐ NO ONE
   - ☐ PSYCHIATRIST
   - ☐ OWN EFFORT
   - ☐ CHURCH
   - ☐ ALCOHOLIC CLINIC
   - ☐ A.A.
   - ☐ PHYSICIAN
   - ☐ OTHER

others who were hospitalized for several weeks did not improve. Further experience and follow-up will be needed to determine the relation of the length of hospitalization to rehabilitation. Factors which favorably influenced recovery were the attitude of the patient toward treatment, readiness to assume responsibility, participation in group activities, acceptance of suggested changes in way of life and, to a lesser extent, the absence of severe physical complications of alcoholism.

There was little difference between the two groups in the number of patients who remained completely abstinent but there was considerable difference in the quality of their recovery. Significantly, the rate of readmission was four times greater in the control group. Some of the control patients had not been drinking since discharge but exhibited few other changes in their way of living. In the study group, several patients remarked about new interests and ability to deal with their problems more realistically, and spoke of being more contented with their lives. Abstinence, which is the most obvious measure of recovery, should not be the only measure of rehabilitation. Abstinence, in fact, can only give the alcoholic freedom to choose his way of life, and therapy should be directed toward helping the patient learn to live more comfortably with himself and with others.

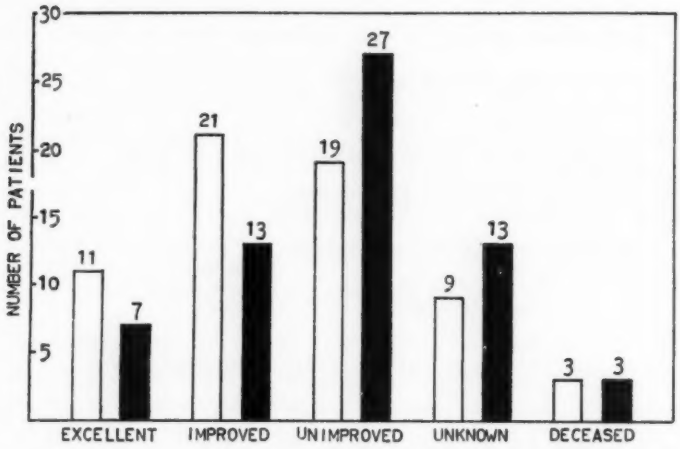

FIGURE 1.—*Comparison of Degree of Improvement in 60 Subjects and 60 Controls 12 Months After Hospitalization.* White bars: subjects. Black bars: controls.

After a few months, several weaknesses were noted in the rehabilitation program. The first was failure of the staff to adapt the pace of the program to the capacity and ability of the patient. Increasing experience showed that many patients were quite limited

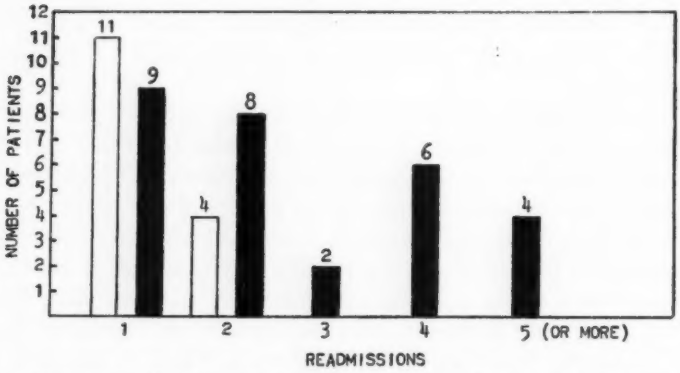

FIGURE 2.—*Number of Readmissions of Subjects and Controls During the 12-Month Period After Initial Discharge.* White bars: subjects (total $N = 51$; total readmissions = 19). Black bars: controls (total $N = 47$; total readmissions = 77). Nine subjects and 13 controls could not be included because they had been lost to contact.

in their ability to comprehend their problems, and their progress was slow. Other patients were so eager to absorb and learn that they were soon obsessed with their recovery and talked, read and thought about nothing but alcoholism. To help overcome these difficulties the program was simplified and the pace slowed. Occupational and recreational activities were strengthened to encourage the development of hobbies and interests and to show the patient how he might resume a more normal relationship with others. For example, a non-alcoholic cocktail hour before dinner exemplified one way in which he could readjust and still observe the usual social amenities.

A greater problem was created by some of the close friendships that developed in group therapy. When properly directed, most of these associations were good, but inevitably there was trouble when several unstable patients became dependent only upon each other after discharge. In order to correct this difficulty, each patient is now asked whether he wishes to have a sponsor in Alcoholics Anonymous and if he does, this is arranged before he returns home. Patients also are reminded not to visit or attempt to help their friends who are drinking excessively and they are asked to continue regular visits to their physician or clinic after discharge from the hospital.

The abuse of sedatives and tranquilizers has also been a problem for certain patients who substitute these drugs for alcohol or use them to supplement their drinking. Five patients in the study group (8 per cent) were habitual or excessive users of barbiturates as well as alcohol. Ten additional patients (16 per cent) had at some time in the past taken an overdose of barbiturates or tranquilizers. Two brought in their own supply of drugs and took them secretly. A few patients became excessively dependent upon barbiturates or meprobamate and resisted any reduction or discontinuance. The alcoholic may use drugs to avoid or postpone the difficult task of changing and rebuilding his life. These medications are extremely helpful but should be used with restraint and an appreciation of their potential danger.

Some patients used the hospital as a further retreat from reality—a cushion between themselves and reality rather than a bridge to help them reach a more normal life. When the patient becomes an active and enthusiastic participant in his own recovery program, a good outcome can be expected. He must be encouraged to make his own decisions and be given the greatest possible freedom to

choose his future course. The therapist should offer suggestions rather than make decisions, but should advise the patient if asked to do so.

In the initial enthusiasm of developing the rehabilitation program, the staff hopefully expected that their wisdom and knowledge would be quickly absorbed and put into use. This did not happen. Some patients learned nothing and remained under care for only a few days. One-third of the study group have so far shown no improvement. The beneficial results of a rehabilitation program, however, may not be apparent at once because new ideas often must be tested by the patient. Recovery seldom occurs at the time the therapist wishes or predicts and months or years may pass before the patient fully accepts what he has learned.

In order to help the alcoholic it is necessary to communicate at his level of understanding and offer suggestions that will assist him to live without dependence upon alcohol. We must listen carefully to his problems and let him know that we care about them. The words we use are less important than our compassion when we say them.

Summary

A program for medical treatment with tranquilizers and sedatives and general counseling of alcoholics in a small private hospital especially devoted to their needs is described. A 12-month follow-up study was made of 60 subjects who had been treated for an average of 14 days with 60 controls from another hospital who received treatment for acute intoxication for an average of 4 days. In the areas of drinking, employment, outside interests, management of problems and continuation of treatment, 11 subjects and 7 controls were rated "excellent"; 21 subjects and 13 controls, "improved." Of the 51 subjects who could be contacted 15 had a total of 19 readmissions; of the 47 controls, 29 had 77 readmissions.

Problems of the hospital's treatment program are described and discussed.

The Treatment of Alcoholics

Martin D. Kissen, M.D.[1]

At the Saul Clinic of St. Luke's Hospital an alcoholic patient is defined simply as one who has lost control of his drinking. Loss of control means that once he has started to drink he cannot stop. This loss of ability to stop drinking may be as insidious as a college man's getting drunk in spite of himself or as overt as the party-goer who drinks everything in sight within the first hour even though he started with the idea that tonight he would take only three drinks. This definition is in general agreement with the idea held by most workers in this country who also agree that there are two components of this disease: psychological and physiological.

There seems to be ample evidence that alcoholism is due to the effect of alcohol on the body, or to the reaction of the body to the ingestion of alcohol. The reasoning behind this is roughly as follows: (*1*) there would be no alcoholism if the patient did not take alcohol into his system; (*2*) there is no evidence of a cure in the sense that a patient once proved to be alcoholic can return to social or "normal" drinking again; (*3*) the alcoholic presents evidence of a true physiological addiction; and (*4*) there is some evidence of differences in the metabolism of alcohol in the alcoholic and the nonalcoholic. On the other hand, it cannot be denied that the alcoholic patient has many and varied psychological problems. Workers in the field disagree on how many of these problems are caused by basic personality and neurotic patterns and how many are the results of alcoholism.

These considerations lead to the logical conclusion that both physiological and psychological methods should be involved in the treatment of alcoholism. The treatment of alcoholic patients must, of necessity, be directed to two distinct entities: alcohol intoxication and its immediate sequels, and alcoholism—the loss of control over drinking. Treatment of the first of these entities is primarily physiological.

[1] Clinical Director, C. Dudley Saul Clinic, St. Luke's Hospital, Philadelphia.

Treatment of Alcohol Intoxication

The objectives of the treatment of alcohol intoxication in patients coming to the clinic at the end of a drinking bout are as follows: (*1*) to get the patient sober as quickly and as painlessly as possible; (*2*) to discover any intercurrent medical or psychiatric complication; and (*3*) to try to make the patient recognize that alcohol has brought him to the clinic or hospital; this might be sufficient to motivate him to begin attending Alcoholics Anonymous meetings, and continue vitamin therapy or the use of tranquilizers as prescribed. He must be made aware that one drink is all that stands between a good productive life and repeated returns to the hospital, or worse. In order to accomplish these objectives, it is very important that the patient be in the best possible condition physically and mentally as soon as possible. Institutionalization of the patient for treatment seems the best way to attain these ends. Although some patients may be able to treat themselves at home, most need a period of insulation in a place where the next drink—which has become so important as to exclude everything else in life—cannot be gotten.

Psychomotor agitation, with symptoms of restlessness, nervousness, insomnia, anorexia, and depression, is one of the most distressing symptoms observed in alcoholic patients during the period of recovery from bouts of acute intoxication. Over the years at the Saul Clinic many substances have been used to alleviate these symptoms because we feel that it is necessary for the patient to be mentally clear and to feel better in order to start the therapy for alcoholism. Chlordiazepoxide hydrochloride[2] has been one of the drugs used for this purpose.

Procedure

On admission to the clinic each patient receives intravenously 1,000 cc. of 10-per-cent glucose in water and 1,000 cc. of 5-per-cent glucose in saline. These solutions contain vitamin B complex. An additional 1,000 cc. of 10-per-cent glucose is given 12 hours later. Each patient is also given, throughout the period of hospitalization, daily intramuscular injections of 100 mg. of thiamin hydrochloride as well as daily oral doses of other vitamin B fractions and ascorbic acid.

Eighty consecutive admissions were selected for this study. All received the routine therapy described above. In addition, the odd-numbered patients were given 100 mg. of chlordiazepoxide either intra-

[2] Librium, Hoffmann–La Roche, Inc.

venously, intramuscularly or by mouth on the day of admission, either at bedtime or, if admitted after 9 P.M., immediately. This was followed up with 10 mg. by mouth four times daily for the remainder of the hospital stay. The even-numbered patients, considered as controls, were given either placebo, other tranquilizers, or sodium amytal and Seconal. The subjective symptoms of psychomotor agitation were measured by observation, at 8-hr. intervals, of sleep, appearance, appetite, tremor, depression and nervousness. Each of these was given a rating of 1, 2 or 3 (good, fair or poor) and the rating was entered on a separate continuous check sheet for each patient.

Results

Figures 1 and 2 show comparisons of the scores of chlordiazepoxide-treated patients and controls. All patients with complications were eliminated from both groups before the scores were totaled.

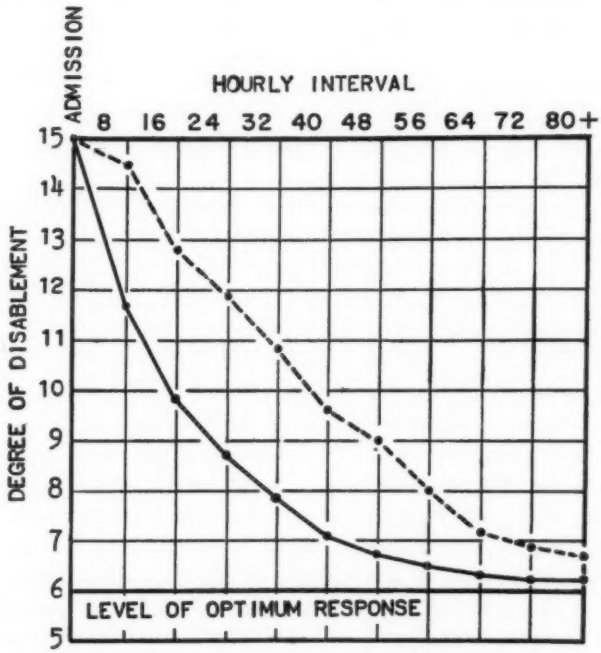

FIGURE 1.—*Average Degree of Disablement in Chlordiazepoxide-Treated and Control Groups Evaluated at 8-Hour Intervals.* Solid line: chlordiazepoxide group. Broken line: control group. For method of determining degree of disablement, see text.

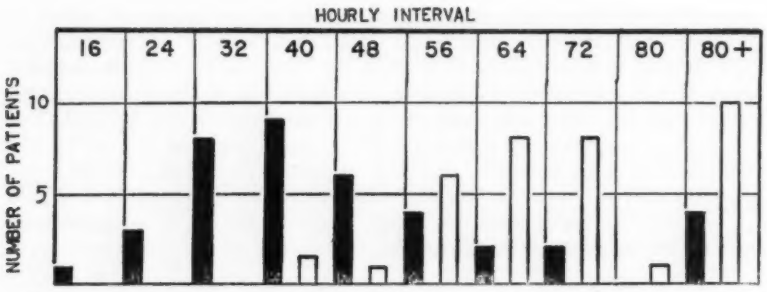

FIGURE 2.—*Number of Chlordiazepoxide-Treated and Control Patients Reaching Optimum Response Ratings During Specified Time Intervals.* Black bars: chlordiazepoxide. White bars: controls.

Figure 1 illustrates the average ratings of subjects and controls at 8-hr. intervals. The worst possible rating would be 18 (a score of 3 on each of the 6 items) and the optimum response would be 6 (a score of 1 on each). Thus the tendency is to approach 6 as treatment continues. The most significant difference is noted at the 8-hr. examination, at which time the curve of the chlordiazepoxide-treated patients dropped by 4.3 while the control curve dropped by 0.5 points.

Figure 2 shows very definitely that the chlordiazepoxide-treated patients arrived at the optimum response level much sooner than the controls. At the examination after 40 hr., 21 (54 per cent) of the subjects, but only 1 control patient, had reached this level. It is interesting to note that within 80 hr., 90 per cent of the subjects but only 72 per cent of the controls were thus helped.

TREATMENT OF ALCOHOLISM

The long-term treatment of alcoholism is directed toward the achievement of three ends which may be labeled identification, surrender and realization.

"Identification" by the patient of himself as an alcoholic is a prerequisite to successful treatment. Simply translated, this means that regardless of the psychological cause of his disease (pathological personality, neurosis or psychopathology of any sort) the patient must relate his actions and attitudes to those of people who are known to be alcoholics.

"Surrender" is the process by which a patient recognizes the physiological implications of alcoholism and accepts the fact that

any time he takes any quantity of alcohol, his particular pattern of binge drinking will follow sooner or later. This, of course, implies rather paradoxically that the only way to defeat the consequences of alcoholism is to surrender to the fact that he cannot ingest any alcohol.

The word "realization" implies complete understanding of the foregoing facts coupled with recognition of the egocentricity of so-called "alcoholic behavior" and of the necessity for creating meaningful social relationships with other people and groups.

Of course, the accomplishment of these objectives requires treatment which is psychiatrically oriented. An understanding of the individual and the dynamics of his relationship to his wife, employer and society in general is indispensable to the supportive psychotherapy which is indicated. Depending on the patient, this may be handled in individual or group therapy. All of this is directed toward proving to the individual that an interesting, constructive and happy life is entirely possible without alcohol.

Postalcoholic Tension State

Tension, best described as anxiety reaction, is an inherent syndrome during the recovery process in patients who remain sober for 1 week to several years. This tension causes many patients to become very uncomfortable and may lead to a resumption of drinking.

It is not necessary to know the specific cause of this anxiety (physical depletion or psychological causes such as resentment or self-pity) in order to produce immediate relief. Chlordiazepoxide in dosages from 10 mg. twice a day to 25 mg. four times a day was used in 67 outpatients, 18 of whom were women, who ranged in age from 24 to 63. The drug was given over periods of 1 week to 6 months and all but 5 subjects reported that their symptoms of anxiety were relieved within 24 hr. No side effects whatsoever were seen in any of the subjects.

An interesting note is the fact that 46 of these patients reported that they had voluntarily reduced the dosage of their medication because they felt so well. This is very important since any type of sedative medication for the alcoholic is usually considered dangerous because of a tendency to increase the dose. Many even become addicted. This is the principal reason why we do not like to use paraldehyde, the barbiturates or chloral hydrate and the bromides.

Summary

The objectives and procedures of treatment of alcoholic patients at the Saul Clinic of St. Luke's Hospital in Philadelphia are described.

In a study of 80 patients admitted consecutively to the clinic, half of whom served as controls, it was found that patients treated with chlordiazepoxide in addition to the regular treatment regimen showed much faster improvement in the areas of sleep, appearance, appetite, tremor, depression and nervousness than did controls. After 40 hours of treatment, 21 subjects and only 1 control received optimal ratings in all these areas.

Chlordiazepoxide was also effective in the management of anxiety in nondrinking alcoholics who were receiving long-term psychotherapy. Of 67 subjects given the drug all but 5 benefited immediately. No side effects were observed.

Evaluation of Drugs in the Treatment of Alcoholics[1]

Keith S. Ditman, M.D.[2]

IT has long been assumed that alcoholism is a treatable condition and the physician is expected to be able to do something about it. Rarely is he called, however, until the condition is far advanced. Drugs are frequently used in the treatment of the symptoms of alcoholism, either alone or in combination with other efforts such as psychotherapy. Specific drug treatment of alcoholism per se is usually not the full intent.

Various assessments have been made of the causes underlying the chronic excessive drinking of the alcoholic but there is no certainty as to the correct answer and there is no reason to conclude even that there is a single entity that should be labeled "alcoholism." Certainly in our present state of knowledge it is premature to call it a "disease." Rather, in view of its behavioral nature, it seems appropriate to view it as a symptom of an underlying disorder, most probably emotional. The escape of the alcoholic into alcoholic euphoria has been viewed by Radó (1–3) as a misguided attempt at self-repair which develops with time into a vicious circle of need, followed by attempted repair, followed by failure and greater need. To say that an alcoholic has a problem is an understatement, and to assume that a drug could contribute significantly to his treatment may not be warranted. Because of his behavior he is usually regarded as unreliable and this characteristic makes his social and economic rehabilitation even more difficult. Hayman (4) has shown that alcoholics are viewed even by psychiatrists as poor treatment risks. One aspect of this unreliability, however, the notorious tendency of alcoholics to drop out of treatment regardless of type, can be used for drug evaluation.

With the increasing number of psychopharmacological agents,

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the need for evaluating drug treatment of the alcoholic becomes ever more important. The present report describes one current method of drug evaluation and some typical results which provide a perspective on the limitations of drug treatment.

PROCEDURE

To approximate the conditions under which most alcoholics are treated by therapists using drugs, alcoholic outpatients were treated in a manner simulating office practice. The aim of the study was to determine the value of various new mood-changing drugs for the alcoholic under these treatment conditions.

Data for the study were collected on two forms filled out at weekly interviews, one by the patient, one jointly by the doctor and a research assistant. These questionnaires were designed to elicit information about the subject's feelings and behavior during the week preceding the interview and about his current condition. The patient's form contained the following items: "I am troubled by poor appetite. I crave alcohol. I have difficulty sleeping. I'm tired during the day. I feel restless. I have the shakes. I feel light-headed or dizzy. I have trouble thinking clearly. I feel sick to my stomach. My sex life is unsatisfactory. My heart races. My future looks black. This past week I was in general: sluggish, unsociable, excitable, unreliable, elated, impatient, touchy, worried, depressed, nervous, lonely, shy, irritable, fearful." Each of these was given one of four ratings by the patient: *No; A little; A lot;* or *Extremely.* He also checked whether he had felt *Fine; Fair; Pretty bad;* or *Terrible* during the week and whether he had felt *Better, No Different* or *Worse* than the week before.[3]

The items on the form were chosen for their appropriateness to the complaints frequent with alcoholics. The items were arranged to correspond with the columns of the last half of an IBM card so that it could be used as an IBM worksheet and the data transposed directly to a card by a key-punch operator.

Items on the second form were designed to identify the patient, his medication and dosage, and to rate him in an impressionistic way as to economic, social, physical, mental and emotional status. There was also space for the physician to record a narrative description of aspects of the patient's progress not included among the items. Data on this form were transposed to the first half of the IBM card.

This method allowed for quantified material to be obtained during the interview from three sources: the patient, the research assistant and the physician. It limited the amount and kind of information obtained, however, and had many other limitations inherent in the brief interview and questionnaire approach. Rosenthal (6) provides a detailed discussion of the merits and limitations of such an approach.

[3] The forms have been published in facsimile in a previous communication (5).

In the present study the problem of the validity of the patient's responses and the observers' ratings cannot be determined with certainty. There is no reason to assume that these items measure the degree of alcoholism in an individual. However, the purpose of this form was only to obtain from an office interview impressions of common symptom categories in order to evaluate the effect of drugs on these symptoms. While alcoholics do complain of mood disturbances, such as anxiety, depression, tension and a sense of worthlessness, hopelessness and loneliness, it has yet to be demonstrated that these are causes of alcoholism, or that the amelioration of these symptoms, if this were possible psychopharmacologically, would alter the course of alcoholism at all.

To test the sensitivity of the questionnaire, the responses at their initial interviews of a group of Skid Row and white-collar alcoholics who showed no signs of having been drinking or of having withdrawal symptoms were compared with responses of a group of nonalcoholics. The nonalcoholic group consisted of individuals coming to a physician's office for their annual physical examination. Known psychiatric patients and alcoholics were excluded. All subjects filled out the patient's form described above. Although the nonalcoholic group came up with a surprising number of mood complaints, both the Skid Row and white-collar alcoholics had more. Furthermore, the Skid Row and white-collar alcoholics had very similar types of complaints. Complaints that differentiated alcoholics from nonalcoholics were: a black future, restlessness, loneliness, depression, worriedness, confusion, nervousness, insomnia, craving for alcohol, and feelings of shyness, sexual dissatisfaction and unsociability. These differences were significant at levels from .01 to .005.

These and other complaints were used in evaluating drug treatments, each patient acting as his own control. In addition, group comparisons were made between patients treated with drug and placebo. Those patients who had alcohol withdrawal symptoms at the time of the initial interview were studied in the same way but were also compared separately.

Results

In the course of this study a number of drugs have been evaluated including phenothiazine and phenothiazine-like tranquilizers, antidepressants, stimulants, anorexiants and milder tranquilizers or sedatives. Results of studies with four different classes of drugs will be given here.

Imipramine[4]

In one double-blind study 116 alcoholic outpatients were treated with imipramine and 79 with a placebo. The 2 groups were appar-

[4] Tofranil, Geigy Pharmaceuticals.

ently adequately matched since comparison of the items on the forms filled out at the initial interviews revealed no significant differences between them.

No significant differences were found between the drop-out rates of the drug and placebo groups. Only 60 per cent of the entire sample returned for the second week of treatment. However, when the drug and placebo groups were split into those who showed signs of alcohol withdrawal and those who had not been drinking at the time of the initial visit, there was a difference in return rates between those given imipramine and those given placebos (Figure 1). Those who had been drinking were more likely to return if given the drug, while those who had not were more likely to return if given the placebo. Using the two-sample Kolmogorov–Smirnov test the significance of this difference was .001. Nondrinking patients who expressed a craving for alcohol were even less likely to return if given the drug.

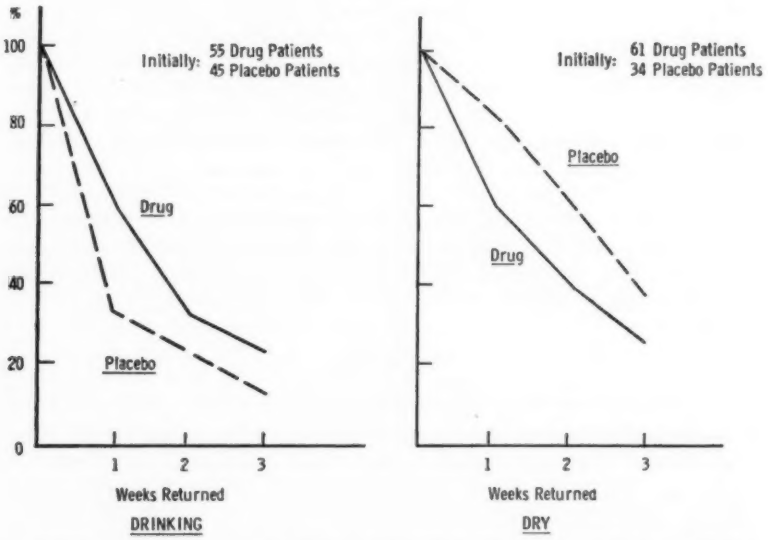

FIGURE 1.—*Percentage of Alcoholics Treated with Imipramine or Placebo who Returned for Weekly Interviews.* Left figure is based on 100 patients who showed symptoms of alcohol withdrawal at the time of the first interview. Right figure is based on 95 patients who had not been drinking at the time of the first interview.

These data indicate that imipramine may have some adverse effect on the alcoholic unless he has withdrawal symptoms. This may be due to the atropinelike side effects of the drug which were frequent. At the end of 1 week of treatment 48 per cent of drug-treated patients, but only 15 per cent of placebo-treated patients, reported side effects. Analysis of the items on the questionnaires did not reveal any other basis for this difference in response.

The above study was based on the hypothesis that the depressed mood that alcoholics frequently report might respond to treatment with an antidepressant drug. The results of this brief study, however, do not validate this hypothesis. The reason for the favorable effect of imipramine on the return rate of alcoholics showing withdrawal symptoms has not been determined.

A group of nonalcoholic depressed patients was also treated with imipramine and compared with the alcoholics who received the drug. These two groups were difficult to distinguish when just the patient-rated questionnaires were compared, although there was a tendency for the nonalcoholic patients to feel more unsociable and complain of a more unsatisfactory sex life. The nonalcoholics were described by the physicians, however, as having more morbid expressions, deeper depressions, less energy and greater impairment of thinking. While none of the alcoholics showed any evidence of psychomotor slowing, many of the other depressed patients did. The nonalcoholics generally responded to imipramine treatment after 3 to 4 weeks. The differences between these patients on questionnaire items and in results of imipramine treatment suggest that there were quantitative and qualitative differences between the depressions of the alcoholic and nonalcoholic patients. The depression of the alcoholics is mild and chronic, while that of the others is more severe and subacute.

Thioridazine[5]

In a study with thioridazine, this drug was found no more effective than the placebo in influencing the return rate of alcoholic outpatients (Figure 2). Although thioridazine did not show any significant advantage over the placebo, patients with more severe complaints who received the placebo were less likely to return than those who received the drug. In addition, patients who rated them-

[5] Mellaril, Sandoz Pharmaceuticals.

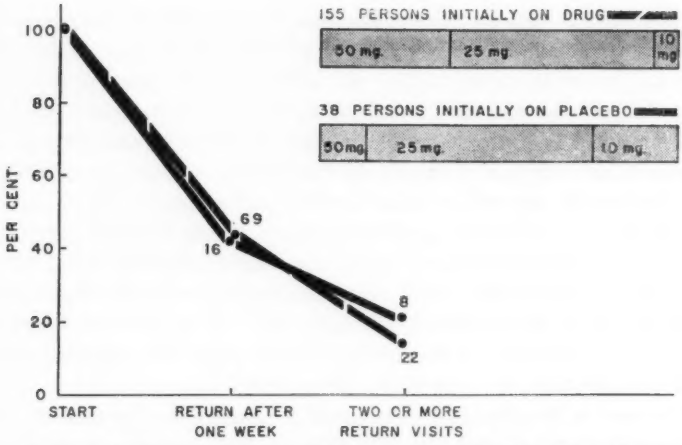

FIGURE 2.—*Percentage of Alcoholics Treated With Thioridazine or Placebo who Returned for Weekly Interviews.* Solid line: patients taking placebo ($N = 38$). Broken line: patients taking thioridazine ($N = 155$).

selves as hostile, irritable, unsociable, and lonely were less likely to return if given the placebo instead of the drug.

From this and other studies using tranquilizers of the phenothiazine group it is our impression that this type of drug has some value in the treatment of symptoms due to acute alcohol withdrawal, but is of little or no value in the treatment of alcoholics who do not have withdrawal symptoms.

Diethylpropion[6]

Diethylpropion was studied to determine whether an anorectic agent might have some damping effect on the alcoholic's drinking, craving for alcohol, smoking or eating. There were no significant differences in the drug- and placebo-treated groups in their reported drinking, craving for alcohol or smoking. Patients taking the drug, however, were less likely to gain weight than those taking the placebo. This difference was particularly true of the patients who were told that the drug might cause loss of appetite. As can be seen in Figure 3, patients given the drug were less likely to return than those given the placebo. The results indicate little promise in treating alcoholics with anorectic agents.

[6] Tenuate, W. S. Merrell Co.

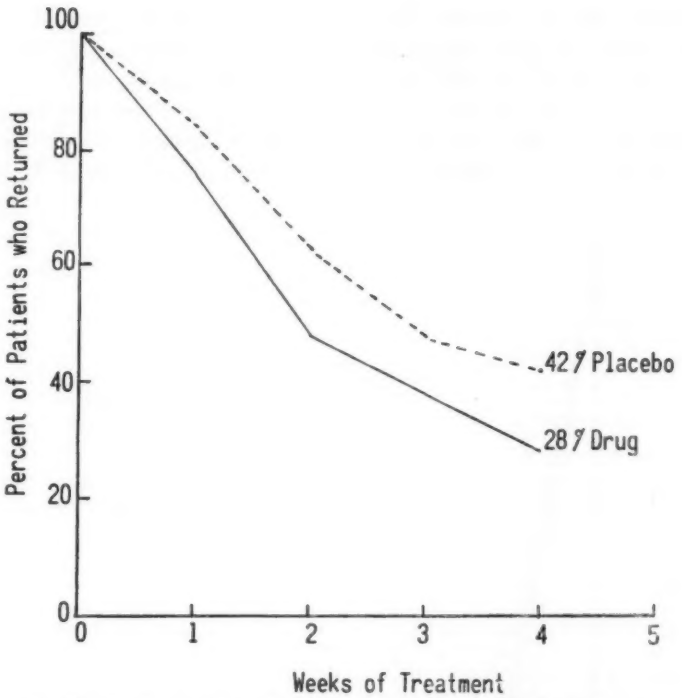

FIGURE 3.—*Percentage of Alcoholics Treated with Diethylpropion or Placebo who Returned for Weekly Interviews.* Solid line: patients taking diethylpropion (N = 29). Broken line: patients taking placebo (N = 19).

Chlordiazepoxide[7]

A controlled double-blind study of chlordiazepoxide was carried out in 214 outpatient alcoholics, half of whom received a placebo. This drug was chosen for study because it was reported to be effective against anxiety, fear, tension and symptoms of alcohol withdrawal. Its effects on the return rate can be seen in Figure 4. This has been the most effective drug as regards return rate of any studied so far in this series. It was equally effective with both Skid Row and white-collar subjects, regardless of whether or not they showed signs of alcohol withdrawal at the initial interview. Analysis of the various items on the patients' questionnaires gave no indi-

[7] Librium, Hoffmann–La Roche, Inc.

cation of why this was so. The physicians' ratings, however, showed more improvement in drug-treated than in placebo-treated patients. It is not known how the physicians were able to discriminate between the drug and the placebo. It may have been statements the patients made about having a feeling of well-being from the drug that guided them. These statements, however, did not find their

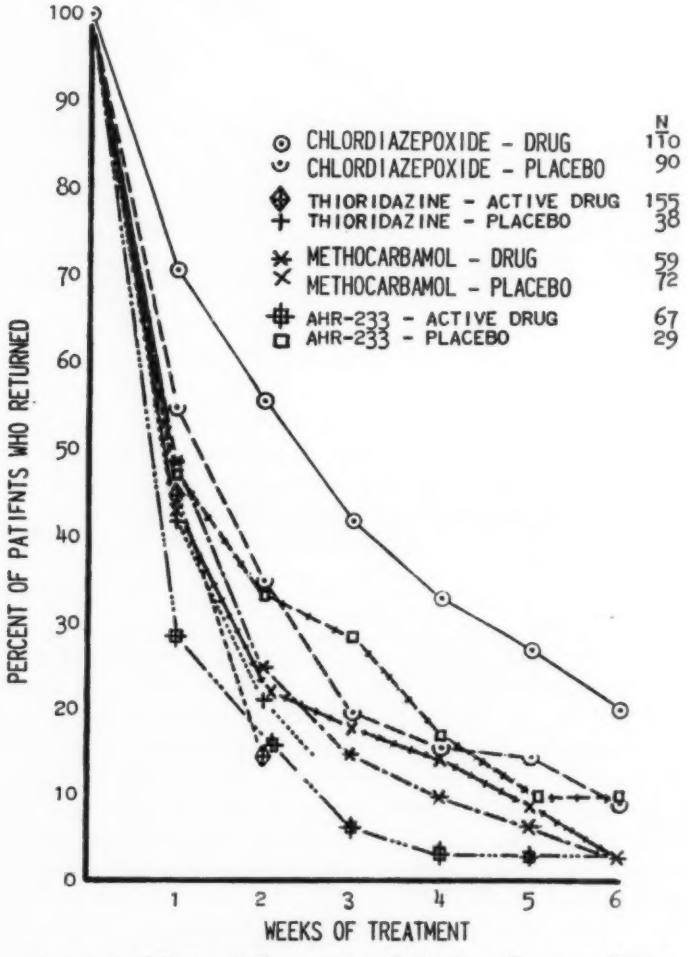

FIGURE 4.—*Effects of Treatment with Various Drugs on Return Rates of Alcoholic Outpatients.*

way into the self-ratings on the patients' questionnaires. On the other hand, the physicians may have been influenced in their ratings of drug effectiveness by the fact that there were more frequent side effects from the drug than from the placebo.

When drug-treated patients whom the physicians rated as improved were compared with drug-treated patients rated as not improved, it was found that the improved patients had rated themselves as more unsociable, shaky, worried, shy and fearful at the start of treatment. It was also noted that Skid Row alcoholics who were given the drug rated themselves more improved after the first week of treatment than did others. This initial advantage over the placebo was lost in subsequent weeks, however.

This study seems to indicate that chlordiazepoxide may have some usefulness initially in brief symptomatic treatment, and in getting the patient to return. Furthermore, the clinical impression drawn from a number of interviews with patients taking chlordiazepoxide was that the drug gave some alcoholic outpatients a sense of well-being and freedom from tension. The following brief case summary gives an example of one such patient.

Mr. L.L., a 50-year-old white married salesman, drank throughout the day and evening because, he said, "It quieted an inner restlessness and made me feel I was more outgoing and functioning better." A number of medications were tried and chlordiazepoxide was his preference. In various studies he had shown little indication of being a "placebo reactor." He was switched back and forth five times from chlordiazepoxide to placebo, and always reported feeling better, less restless and more outgoing when taking the drug. After taking 100 mg. of chlordiazepoxide daily for nearly 4 months, medication was stopped. He reacted to this by starting to drink again on the same day. No withdrawal effects from the medication had had time to develop. A week later he no longer had the sense of well-being and freedom from restlessness that he had had while taking the drug.

Discussion

There are a number of difficulties in evaluating a treatment for alcoholism. The condition is not well understood and there are no reliable short-term criteria by which to gauge improvement. Although alcoholics apparently have more mood and symptom complaints than nonalcoholics, the relationship of these complaints to the alcoholism is unknown. Furthermore, the very nature of these complaints makes them unreliable for the evaluation of symptomatic

treatment. They are subjective and at times ephemeral, and can be altered by many of the things that happen in the patient's life. Although the attempt to quantitate aspects of the clinical approach for statistical handling has been found to have many limitations, it seems likely that it can be refined and that, with more careful application, some of the changes not induced by drugs, which reduce the sensitivity of the method, can be weeded out. At present, the evidence indicates that drugs are of limited value in the symptomatic treatment of alcoholics, and there is no evidence to indicate that they are of value in the treatment of alcoholism as an entity.

Summary

A method of evaluation of drug treatment of alcoholic outpatients, based on the rate of return for weekly therapeutic interviews and on triple ratings of drug effects by patient, physician and a research assistant, is described. Four drugs, imipramine, thioridazine, diethylpropion and chlordiazepoxide, were evaluated by this method in studies using placebos. The results indicated that only one, chlordiazepoxide, was beneficial in the treatment of the alcoholics and only to a limited extent. It is concluded that drugs are of limited value in the symptomatic treatment of alcoholics and that there is no evidence to indicate that they are of value in the treatment of alcoholism as an entity.

REFERENCES

1. Radó, S. The psychic effects of intoxicants: an attempt to evolve a psychoanalytical theory of morbid cravings. Int. J. Psychoanal. 7: 396–413, 1926.
2. Radó, S. Psychoanalysis of pharmacothymia (drug addiction). Psychoanal. Quart. 2: 1–23, 1933.
3. Radó, S. Narcotic bondage, a general theory of the dependence on narcotic drugs. Amer. J. Psychiat. 114: 165–170, 1957.
4. Hayman, M. Current attitudes to alcoholism of psychiatrists in Southern California. Amer. J. Psychiat. 112: 485–493, 1956.
5. Ditman, K. S. and Cohen, S. Evaluation of drugs in the treatment of alcoholism. Quart. J. Stud. Alc. 20: 573–576, 1959.
6. Rosenthal, D. Drug research design in a psychiatric outpatient setting. In: Cole, J. D. and Gerard, R. W., eds. Psychopharmacology, Problems in Evaluation; pp. 434–446. Washington, D. C.; National Research Council; 1956.

The Outpatient Management of the Alcoholic

Fred E. Lawrence, M.D.[1]

OUR ABILITY to treat alcoholism effectively is limited by the fact that it is a disease process with multiple etiological factors which are often obscure, ill-defined and poorly understood. Moreover, as Jellinek (1) has recently pointed out, we have categorized under the term alcoholism a number of different syndromes some of which merit being considered as disease processes in their own right and some of which are merely symptomatic of other diseases. Since Jellinek's classification has important implications for the therapy of alcoholism, it will be outlined briefly here.

Types of Alcoholism

Using a simple operational definition of alcoholism—the use of alcoholic beverages that causes any damage to the individual or to society or both—Jellinek describes five different types of alcoholism. These five do not necessarily encompass all alcoholism but they are the types that it is possible to delimit in the present state of our knowledge.

1. Alpha alcoholism is a purely psychological continual dependence on alcohol to relieve physical or emotional pain. There is no loss of control or inability to abstain from alcohol.

2. In beta alcoholism medical complications from the excessive use of alcohol occur but there is neither physiological nor psychological dependence.

3. Gamma alcoholism, the type most commonly encountered in the United States, is characterized by withdrawal symptoms and by loss of control over the ability to use alcohol. Damage to the

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individual's health, interpersonal relationships and economic life is greater than in other types of alcoholism.

4. Delta alcoholism is also characterized by withdrawal symptoms, but instead of loss of control there is an inability to abstain from the use of alcohol. Within certain limits the drinker is able to regulate his intake but he must drink regularly.

5. Periodic alcoholism is designated as epsilon alcoholism in Jellinek's classification.

While all of these types of alcoholism are encountered clinically the majority of cases are of the gamma type. In my own experience the alpha type is not rare and is encountered more frequently in private than in clinic practice. Delta alcoholism is quite rare in this country but can be observed occasionally if one is alert to its existence.

The salient feature distinguishing the gamma alcoholic from other users of alcoholic beverages is loss of control over the use of alcohol. The social drinker is able consistently to take one drink or several and stop whenever he desires to do so. In gamma alcoholism, on the other hand, the initial use of alcohol triggers, with greater or lesser frequency, episodes of uncontrolled drinking which may go on until the individual is so ill, inebriated or destitute that he is unable to continue drinking.

As the clinician sees it, this process of loss of control is a very real entity; however, it is one about which there is little scientific knowledge. Once established, it appears to be permanent and irreversible. It is likely that this is a complex psychophysiological process which may ultimately prove to be similar or identical in nature with the process of addiction to other drugs.

The criteria of an addiction-producing drug are that its continued use leads to the development of the following three conditions: (*1*) physiological and psychological dependence, (2) withdrawal symptoms, and (*3*) tolerance. Alcohol fails to meet only the last of these criteria. Because of the inability of the liver to metabolize more than 10 to 15 ml. of absolute alcohol per hour, tolerance cannot develop. Except for this, gamma and delta alcoholism may well be considered as addictions. The work of Rayport (2) further highlights the relationship of alcohol to the addictive drugs, emphasizing as it does the increased vulnerability of some arrested alcoholics to narcotic addiction. Jellinek suggests that in

America, where the therapist is primarily concerned with gamma alcoholism, research should center around the pharmacological process of addiction.

Problems in Treatment

Recognizing that there are a number of different types of alcoholism, that there is no specific etiological agent against which a magic bullet might be devised, and that, at least in gamma alcoholism, we are dealing with an addictive process, how are we to go about treating the alcoholic?

The estimated 4 or 5 million alcoholics in the United States constitute a health problem that cannot be ignored. Since alcoholism occurs in all social, economic and occupational groups it must be treated not only by the specialist and by the public agency but also by those in the general practice of medicine. Actually the latter are frequently in the most favorable position to detect its presence and to take effective steps to initiate treatment.

Alcoholism, whatever its type, is a protracted chronic disorder. Many alcoholics whose alcoholism eventually is arrested do not resolve their drinking problems until a number of years after they first seek treatment. In the interval the physician may be called on repeatedly to deal with the medical problems created by the patient's use of alcohol.

The success of any method of treatment of the alcoholic depends in large measure on the development of an effective therapeutic relationship. The physician must have the conviction that the alcoholic is suffering from a treatable illness and that he has the necessary therapeutic skills to deal with that illness.

This is not easy. When the alcoholic first presents himself for treatment he is usually under the influence of alcohol, experiencing withdrawal symptoms, or both. Frequently he comes not of his own volition but rather at the insistence of his family or employer, or in response to some economic or legal pressure. He cannot generally be regarded as well motivated. When first seen by the physician the severity of the patient's symptoms often obscures any underlying psychiatric disorder so that the existence or the severity of the latter cannot be evaluated. His condition may make it difficult to obtain an adequate history and his uncooperativeness may interfere with physical examination.

Several problems confront the physician at this point. He must

bring the patient's withdrawal symptoms under control, obtain his cooperation, evaluate his physical and mental status, bring about a cessation of the patient's drinking, and establish a therapeutic relationship which will ensure that the patient will return for further treatment.

While it is sometimes desirable and even essential that the alcoholic be cared for in the hospital, the definitive treatment of the vast majority should occur at the outpatient level. In the last analysis the alcoholic must be able to function as a member of organized society and to remain abstinent from alcohol within the environment of that society if his alcoholism is to be arrested. The decision to hospitalize the alcoholic patient should not be made without carefully considering his social, economic and psychiatric needs as well as the medical symptoms. Frequently the alcoholic patient is maintaining a very tenuous adjustment that may be broken by a relatively brief period of hospitalization and be extremely difficult to restore. Protracted hospitalization, especially when it occurs in mental hospitals, cannot always be depended on even to assure abstinence from alcohol during the period of hospitalization and may cause the patient to regress into a more dependent state. As a general rule, then, if there are no pressing medical indications for hospital care, treatment of the alcoholic should begin at the outpatient level and only those patients should be hospitalized who have failed to improve after intensive outpatient treatment or who in the course of such treatment develop medical or psychiatric problems requiring inpatient care.

Such an approach makes it essential that the presenting symptoms of the alcoholic as he enters treatment be dealt with promptly and effectively.

Psychopharmacological Agents

The major psychopharmacological developments of the past several years have been investigated promptly for their possible usefulness in the treatment of alcoholism. The value of the rauwolfia derivatives has been established by studies such as those of Avol and Vogel (3) and Neuer (4). Numerous investigations (5–8) have clearly demonstrated the value of the phenothiazines.

While they represent major advances in the therapy of alcoholic psychoses and withdrawal symptoms, the phenothiazines and the rauwolfia derivatives are not free of disturbing side effects. These

have been summarized recently by Hollister (9, 10). Adverse behavioral effects are quite rare, as are extrapyramidal symptoms from the phenothiazines, especially if the latter are used for only short periods of time. Jaundice and agranulocytosis are most unlikely to occur from the use of phenothiazines in the short-term treatment of the alcoholic. However, the tendency of both groups of drugs to potentiate underlying convulsive tendencies is an undesirable feature where they are to be used in the alcoholic. Hypotensive reactions may be a serious hazard and may sometimes limit the usefulness of the drugs in the outpatient. In addition, the rauwolfia derivatives may activate peptic ulcer.

Antidepressants

The incidence of depressive symptomatology in alcoholics has become increasingly apparent as a higher percentage of cases is kept under observation sufficiently long to permit adequate psychiatric evaluation. Depression may be reactive in nature, a consequence of the many traumatic experiences the patient has undergone. On the other hand, alcoholism may occur as a symptom of manic–depressive or involutional depressions. The increased incidence of suicide in the alcoholic has been emphasized by Robins and his co-workers (11) and by Ayd (12). Where the risk of suicide is apparent, hospital care is imperative. However, a number of the less severe depressions are amenable to outpatient treatment.

Some of these depressive reactions may respond favorably to chlordiazepoxide (discussed below). Others require the use of other antidepressants. At present two important groups of drugs are available for this purpose. One group is represented by imipramine[2] and amitriptyline.[3] The former has proved effective in some cases, the latter has not been available long enough to permit its evaluation.

The monoamine oxidase inhibitors comprise the second group. These may be divided into hydrazine and nonhydrazine agents. The possibility of liver damage from the hydrazine type of inhibitors requires that they be used with great care in the alcoholic, where an already damaged liver may be present. The nonhydrazine inhibitors theoretically should be safer agents for use in the alco-

[2] Tofranil, Geigy.
[3] Elavil, Merck, Sharp & Dohme.

holic. One of these, alpha-ethyltryptamine,[4] has shown promise of being a safe, effective antidepressant in the alcoholic (13). Another, tranylcypromine,[5] has not yet been adequately evaluated in the depressed alcoholic. It acts rapidly in a high percentage of cases. The incidence of orthostatic hypotension appears to be significant and it has definite amphetamine-like side effects which may prove to be undesirable in the alcoholic.

Ayd (14) has described the undesirable reactions to antidepressant drugs. These have been toxic psychokinetic reactions similar in nature to the excitatory effects of the amphetamines and severe, even fatal, somatic reactions where imipramine is used concurrently with one or another monoamine oxidase inhibitor. He emphasizes the necessity of limiting the amount of these drugs prescribed and of not permitting refills. In alcoholism, where it can be anticipated that a significant number of patients will demonstrate, with any active psychopharmacological agent, the same lack of control they have shown with alcohol, these precautions cannot be stressed too strongly.

Chlordiazepoxide[6]

A new drug, chlordiazepoxide, became available for investigation at the Indiana Division of Mental Health in January 1960. Experience with its use since that time in over 500 clinic and private alcoholic patients has been reported in part in previous papers (15, 16) and will be summarized briefly here.

Procedure

The effectiveness of chlordiazepoxide in the management of alcohol withdrawal symptoms was evaluated in 200 consecutive admissions to the Central Indiana Alcoholism Clinic. This group showed considerably more socioeconomic deterioration than might be expected in private patients seen in general practice. For example, only 75 were employed, only 80 were married and not all of the latter were living in organized families. On arrival at the clinic, 25 of the patients were sober and were not experiencing withdrawal symptoms; 69 were sober but were having alcohol withdrawal symptoms; and 106 were under the influence of alcohol and were having, or subsequently developed, withdrawal symptoms.

[4] Monase, Upjohn.
[5] Parnate, Smith, Kline & French.
[6] Librium, Hoffmann–La Roche, Inc.

Results and Discussion

The results of treatment with chlordiazepoxide in the 175 patients who experienced withdrawal symptoms can be seen in Table 1. The results of Ticktin and Schultz (17), reporting the effectiveness of chlordiazepoxide in acutely agitated alcoholics, had not been published when our study began. Our experience confirmed the value of this drug in such patients and further indicated its usefulness in alcoholics with less severe withdrawal symptoms.

Especially when chlordiazepoxide was given parenterally, a number of restless, disturbed or even incoherent patients experienced prompt relief of these symptoms, making it possible to obtain adequate histories or to perform physical examinations which the condition of the patient would not otherwise have permitted. Clinically there often appeared to be a sobering effect on the patient. Within a few minutes after adequate parenteral doses, or within half an hour to an hour after oral medication, even severely agitated patients showed quite marked relief of their symptoms and were then able to cooperate in their treatment.

In addition to its usefulness in the control of acute alcoholic psychoses, this drug in two cases in our series proved valuable in treating chronic auditory hallucinosis. Both of these patients, elderly men with long histories of alcoholism, remained free of hallucinations as long as they were under treatment with chlordiazepoxide.

TABLE 1.—*Degree of Severity of Withdrawal Symptoms and Degree of Relief from Symptoms in 175 Alcoholic Patients Treated with Chlordiazepoxide*

SEVERITY OF SYMPTOMS*	DEGREE OF RELIEF†						
	Unknown	*None*	*1+*	*2+*	*3+*	*4+*	*Totals*
1+	6	1	1	0	0	11	19
2+	17	1	1	2	9	52	82
3+	7	1	1	4	9	45	67
4+	0	0	0	2	0	5	7
Totals	*30*	*3*	*3*	*8*	*18*	*113*	*175*

* Criteria were as follows: 1+ = Mild tremulousness, restlessness and insomnia. 2+ = Moderate tremulousness, anxiety, anorexia, nausea and insomnia. 3+ = Marked tremulousness, psychomotor restlessness, severe anorexia, nausea, vomiting, impending delirium tremens or impending acute hallucinosis. 4+ = Delirium tremens or acute hallucinosis.

† Criteria were as follows: None = Patient continued drinking and was lost to treatment after two or three visits. 1+ = Complete relief of symptoms requiring longer than 96 hr.; additional medication needed to control insomnia or vomiting. 2+ = Same as 1+ but no additional medication needed. 3+ = Marked to moderate relief of symptoms following administration of drug; complete relief within 48 to 96 hr. 4+ = Marked relief of symptoms following administration of drug; complete relief within 24 to 48 hr.

Furthermore, no patient in our series to date has experienced convulsions once treatment with chlordiazepoxide was instituted. This will probably not prove to be the case in studies of large groups of acute alcoholic psychoses but the use of chlordiazepoxide markedly reduced the need for additional anticonvulsant medication.

A number of patients in this series suffered from chronic anxiety states and were using alcohol for the relief of anxiety symptoms. Some of these could be considered as alpha alcoholics. In these cases chlordiazepoxide was continued beyond the time necessary to control withdrawal symptoms. Where anxiety was effectively controlled, the patients frequently abandoned the use of alcohol or reduced their intake markedly. This is illustrated by the following case.

A 44-year-old unmarried female domestic servant was admitted to the clinic on 17 June 1960. She gave a history of phobic anxiety reaction beginning in her mid-twenties and becoming progressively more severe during the following years. At the time of intake she was afraid of being alone, of crossing streets, of being in crowds, of riding elevators and of being in high places. Several years before she had discovered that alcohol was helpful in relieving her fears and had gradually increased her intake until she was consuming between ½ and 1 pint of gin or vodka daily. She had been treated by a private physician with sedatives and phenothiazines without significant improvement.

Chlordiazepoxide was prescribed in a dosage of 10 mg. before each meal and 20 mg. at bedtime. Three days later she reported a marked diminution of her phobic anxiety reactions and had ceased using alcohol. She was still unable, however, to cross a street alone. The dosage was increased to 25 mg. four times daily. This was subsequently reduced to 25 mg. every 8 hours. The latter dosage was continued up to the time of the present report and the patient has been functioning freely without anxiety and without dependence on alcohol. She has been gainfully employed for several months. A complete blood count on 25 April 1961 was entirely within normal limits. She was seen last on 23 May 1961.

A few patients with depressive states also responded well to chlordiazepoxide. The following case is an example of this group:

A 50-year-old widowed salesman was admitted to the clinic on 25 March 1960. He gave a history of heavy but controlled social drinking from the age of 30. When he was 46 his wife died after a protracted illness. At that time his drinking became excessive and uncontrolled. A few months later he received a course of electroshock treatment in a private psychiatric hospital for a reactive depression. From that time until admission to the clinic he gave a history of steady excessive drink-

ing with superimposed sprees. His weight had dropped 50 pounds. He complained of anorexia, severe insomnia and nervousness. He showed severe tremor, moderate restlessness and marked palmar hyperhidrosis, and appeared quite depressed.

Chlordiazepoxide was prescribed in a dosage of 50 mg. before each meal and at bedtime. The patient was not seen for 3 days because of an intervening weekend. He then stated spontaneously that he "felt one hundred per cent better"; his withdrawal symptoms had subsided after the initial dose of the drug and were completely controlled within 24 hr. Two days later he appeared less depressed and reported being in better spirits.

In subsequent treatment the dosage was gradually reduced to 10 mg. three times daily. The patient remained free of depression, used no alcohol and was able to work effectively until he discontinued treatment in September 1960. In retrospect he believed that he had been chronically depressed since the death of his wife and that during treatment he had for the first time since that event recovered his normal spirits.

An additional finding of considerable importance in the therapy of the alcoholic was noted in that group of patients where continued treatment with chlordiazepoxide was indicated. It was possible to establish a much more effective therapeutic relationship with many of these patients than had previously been the case. A number of them had been treated before and the earlier experience could be used as a base line for comparison. The chlordiazepoxide patients were in general more productive in interviews and appeared to have a greater capacity for objective appraisal of their problems and of their life situations. The therapeutic process, whether individual psychotherapy, social casework or group therapy, appeared to be more meaningful to the patient.

During 1959 the Central Indiana Alcoholism Clinic averaged 30 new patients and 161 patient interviews monthly. In the year following the initial use of chlordiazepoxide the monthly average of new patients was 34 and of patient interviews 403. For the first 3 months of 1961 the respective averages were 30 and 437. In large measure the increase in the number of patient interviews was due to the fact that a significantly greater number of patients whose withdrawal symptoms were treated with this drug remained in continuing therapy, compared with any prior treatment method. This experience suggests that chlordiazepoxide will become the drug of choice in the management of many of the alcoholic psychoses and in the relief of alcohol withdrawal symptoms. In adequate dosages

it has a specific action against alcoholic hallucinations, psychomotor restlessness, tremor and anxiety. When the drug is administered parenterally, nausea and vomiting are promptly controlled in the majority of cases.

Dosage requirements in the outpatient present a difficult problem. It is apparent that larger quantities of the drug are required in the alcoholic than in the nonalcoholic patient. There is, however, marked individual variation in dosage requirement, which appears to be related not to body weight but to severity of symptoms and which frequently lessens as the patient's condition improves. Where possible it is helpful to keep the patient under observation for 3 or 4 hr. after an initial oral dose of 25 to 50 mg., since the response may be a valuable guide to further dosage requirements. It is highly desirable that the patient be seen daily in order that the necessary dosage adjustments can be made.

Side effects, drowsiness and occasional mild ataxia may occur as the result of excessive dosage but at times these appear to be inevitable if enough of the drug is given to control the patient's symptoms. In the outpatient these side effects do not present a serious problem if a responsible relative or friend can be depended on to keep the patient under observation. Where there is no one to assume this responsibility more conservative dosages must be employed.

The emphasis in this paper has been on the use of various psychopharmacological agents which may be of value in alcoholism. However, it is not intended that these drugs be used as substitutes for the basic therapies of alcoholism—individual and group psychotherapy, Alcoholics Anonymous, pastoral counseling and the use of chemical barriers such as disulfiram[7] or citrated calcium carbimide.[8] Used properly, psychopharmacological agents may be extremely valuable adjuncts in the treatment of alcoholism but they do not replace other methods of treatment.

Summary

Types of alcoholism and problems in treating alcoholics are discussed.

Methods of treatment of outpatient alcoholics are described and discussed with emphasis on the use of psychopharmacological

[7] Antabuse, Ayerst.
[8] Temposil, Lederle.

agents, including rauwolfia derivatives, phenothiazines, imipramine, amitriptyline, monoamine oxidase inhibitors and, particularly, chlordiazepoxide.

In a study of 175 alcoholic patients experiencing withdrawal symptoms of varying severity from mild tremulousness to delirium tremens and acute hallucinosis, 113 showed marked relief of symptoms on administration of chlordiazepoxide and complete relief within 48 hours.

Patients treated with this drug were able to establish more effective therapeutic relationships than with other medications previously tried. They became more productive in interviews and more objective in their appraisal of their problems. By controlling withdrawal symptoms the drug made earlier establishment of the therapeutic relationship possible. Chlordiazepoxide was of value in treating chronic auditory hallucinosis, as an anticonvulsant, and in controlling chronic anxiety and depressive states.

Dosage requirements are discussed and two case histories are given.

REFERENCES

1. Jellinek, E. M. The Disease Concept of Alcoholism. New Haven; Hillhouse Press; 1960.
2. Rayport, M. Experience in the management of patients medically addicted to narcotics. J. Amer. med. Ass. **156**: 684–691, 1954.
3. Avol, M. and Vogel, P. J. Treatment of delirium tremens with reserpine (Serpasil). A preliminary report. J. Amer. med. Ass. **159**: 1516–1520, 1955.
4. Neuer, H. Serpasil in the treatment of acute alcoholic psychoses. Ohio St. med. J. **51**: 749–751, 1955.
5. Albert, S. N., Rea, E. L., Duverney, C. A., Shea, J. and Fazekas, J. F. Use of chlorpromazine in the treatment of acute alcoholism. Med. Ann. D.C. **23**: 245–247, 1954.
6. Schultz, J. D., Rea, E. L., Fazekas, J. F. and Shea, J. Chlorpromazine in the management of acute alcoholic states. Quart. J. Stud. Alc. **16**: 245–250, 1955.
7. Fazekas, J. F., Shea, J. and Rea, E. Use of chlorpromazine in the management of acute and postalcoholic states. Int. Rec. Med. **168**: 333–339, 1955.
8. Mitchell, E. H. Treatment of acute alcoholism with promazine (Sparine). J. Amer. med. Ass. **161**: 44–45, 1956.
9. Hollister, L. E. Current concepts in therapy. Complications from psychotherapeutic drugs. *I.* New Engl. J. Med. **264**: 291–293, 1961.
10. Hollister, L. E. Current concepts in therapy. Complications from psychotherapeutic drugs. *II.* New Engl. J. Med. **264**: 345–347, 1961.
11. Robins, E., Murphy, G. E., Wilkinson, R. H., Jr., Gassner, S. and Kayes, J. Some clinical considerations in the prevention of suicide based on a study of 134 successful suicides. Amer. J. publ. Hlth **49**: 888–899, 1959.
12. Ayd, F. J., Jr. Suicide, a hazard in depression. J. Neuropsychiat. (Suppl.) **2**: 52–54, 1961.

13. Lawrence, F. E. Alpha-ethyltryptamine acetate in alcoholism. A preliminary report. J. Neuropsychiat. (Suppl.) 2: 88–90, 1961.
14. Ayd, F. J., Jr. Toxic somatic and psychopathologic reactions to antidepressant drugs. J. Neuropsychiat. (Suppl.) 2: 119–122, 1961.
15. Lawrence, F. E., Johnson, J. M., Webster, A. P. and Schwartz, L. Chlordiazepoxide in the treatment of alcoholism. J. Neuropsychiat. 2: 93–100, 1960.
16. Lawrence, F. E. Some Recent Advances in the Medical Management of Alcoholism. Read at the 13th Annual Scientific Assembly, Illinois Academy of General Practice, Chicago, 27–29 September 1960.
17. Tickтin, H. E. and Schultz, J. D. Librium, a new quieting drug for hyperactive alcoholic and psychotic patients. Preliminary Study. Dis. Nerv. Syst. (Suppl.) 21: 49–52, 1960.

Problems in the Treatment of the Alcoholic

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TWO PRIMARY PROBLEMS in the treatment of the alcoholic are getting the patient to agree to the diagnosis and persuading him to accept treatment. Unless these two ends are reached or at least approached, the results with any type of treatment are doomed to be something less than dramatic.

Acceptance of Diagnosis

Considering first the patient's reluctance to agree with the diagnosis, it is reasonable to ask what makes the idea so unacceptable. One factor is the loss of self-esteem the patient suffers if he agrees and then continues to drink. As long as he denies the illness he ostensibly preserves his status as a nonalcoholic and has no real reason to abstain—except temporarily.

It may be difficult to understand how the patient can continue to regard himself as a nonalcoholic in view of his drinking behavior; but this paradox is resolved by his definition of an alcoholic, which always excludes him. The exclusion is comfortably accomplished by taking some one facet of the problem, which he lacks, as essential to the diagnosis. For example, the patient who habitually drinks in bars says, "I never drink alone." The alcoholic who drinks alone says, "I never drink in the morning." Perhaps the most widely used rationalizations are, "I drink like anybody else," or, "I only drink beer and never touch the 'hard stuff,' therefore I'm not an alcoholic."

This is rather normal thinking. It is the same type of mentally economical explanation that the obese person or the heavy smoker utilizes. The obese plan to diet if they gain any more weight and they certainly know people who are fatter than they are. Similarly, the heavy smoker may continuously plan to "cut down" on his intake or he may smoke a box of cigars each day instead of cigarettes.

If the patient agrees that he is an alcoholic and then continues to drink, he admits that he has lost control over his intake, literally,

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that he has to have alcohol in excess to continue to function. Such an admission destroys much of his rationalization system. His endlessly repeated assurances to the family, "If my drinking gets any worse, I'll do something about it," or the classical "I can take it or leave it alone," cease to make any sense, even to himself. It is generally agreed that an alcoholic cannot "take it or leave it alone." If he agrees that he is an alcoholic, there is no need to delay treatment until things get worse; the term implies that things are already at their worst.

Another factor in the reluctance to agree is that while most diagnoses are impersonal names for unfortunate events which may occur to a patient, alcoholism is an exception. Since most of the 70 million social drinkers in the country regard a drink or two as a pleasant experience, they presume that the alcoholic has a similar response. Since no one forced the alcohol down his gullet, he only got what excessive indulgence deserves and they blame and condemn him for his alcoholism.

It would be worth while to know what the term "alcoholic" means to the public and on what this opinion is based. To many it means an unreliable though pleasant human who is frequently absent from work; to others the term may connote a Skid Row derelict, synonymous with total failure, a "bum." Whatever it means, it is not a desirable title.

Since it is no longer fashionable to stress character as a virtue, the public is less likely than in the past to consider alcoholism a "weakness of character." If character is defined as moral vigor acquired through self-discipline, lack of it may be offered by some as an etiological factor.

Being a member of the responsive public, the alcoholic shares the general derogatory view of the diagnosis and for most of his drinking career refuses to apply it to himself. The suggestion to a patient who has recovered from a severe bout of delirium that he talk to a member of Alcoholics Anonymous will often bring the reply that he "doesn't want anything to do with a bunch of drunks."

At this point a word must be said for the fellowship of Alcoholics Anonymous. Its members have become associated with two very favorable views in the public mind. First, they are making a sincere effort to maintain sobriety; and second, they are helping others with similar problems. These ideas are so firmly planted in the minds of many that an active member of Alcoholics Anonymous

may no longer be considered an alcoholic but an "A.A." And it is encouraging to note that the stigma often associated with the alcoholic is not applied with the same vigor to an "A.A." Rather, he is more admired for his recovery than damned for his illness.

Acceptance of Treatment

Obviously, if the patient denies the diagnosis there is no internal reason for accepting treatment. Although he may reluctantly agree to see a physician under pressures exerted by his wife or employer, it can be anticipated that when these external forces abate so will the patient's interest in treatment.

It is worth while to consider what treatment means to the alcoholic as compared with medical treatment in general. In most sickness, treatment implies relief; and the more effective the treatment the more prolonged the relief. If the treatment is specific the improvement may even be so lasting as to be obvious if a follow-up is done. But the alcoholic may see treatment as a deprivation which, he fears, he will be unable to endure. It may mean the loss of the very glue with which he is stuck together. Effective treatment implies a permanent loss of the substance which to most alcoholics apparently is life's most precious offering. Many such patients will give up wife, family, friends and job before they will seriously consider giving up alcohol.

The Role of Drinking

This degree of reluctance to relinquish this drug is not understandable on the basis of the taste of alcohol, the brief euphoria or even the extended oblivion it may produce. This tenacious refusal to give up alcohol, only after most else is lost, can only be understood in the light of the relationship of drinking to these other aspects of the patient's life. If alcoholism is a chronic insidious process requiring years to become manifest, then the successes as well as the failures during this prolonged interval of increasing disability may have occurred as a part of the illness.

For instance, the patient's marriage may be a direct result of his drinking. He may not have been too clear when he made his decision or took his vows. Subsequently, he may have intended to obtain a divorce but was never sober long enough to carry out all the necessary legal steps. If he has to make a choice between alcohol

and his wife, the decision to continue drinking may be implicit in the relationship.

In other situations the marriage may be continued because the wife supplies the alcohol. In some instances a complete reversal of the usual marital roles may occur, i.e., the wife works, the husband runs the household, does all the cooking, and most of the drinking. It may require a year or more to bring this change about, but once it happens, the couple may be much more compatible. If the wife in such a circumstance decides that her husband is better off sober and refuses to supply him with any more alcohol, she will shortly be without a spouse.

In another type of marriage, the husband is aggressive and successful and the wife is reticent and socially inadequate. She may be unable to tolerate the social demands he makes on her without recourse to a few drinks. The amounts she consumes may increase rather rapidly. Over a period of several years she has a series of embarrassing experiences and finally gives up attempting to socialize, but she does not give up the alcohol. In one such case the husband described his wife as follows: "She's always taking a drink to 'get ready to go somewhere' and she hasn't been out of the house in a year." This marriage was incompatible from the beginning, but the wife succeeded in complying for a few years by relying on alcohol, until she became totally unable to control her drinking. In the meantime the couple had children and had acquired other community property which tended to prolong the relationship. Such a marriage is seldom destroyed because of the drinking; rather, it is formed and endures as a manifestation of the alcoholism.

A similar situation may apply in the patient's work. For example, an extremely able and successful attorney was seen after his legal practice, his marriage and his resources had slowly dissolved in an alcoholic fog. To all intents and purposes his alcoholism had destroyed him. But his history showed the following: After finishing well up in his class in law school, he found it next to impossible to present his cases before a judge and jury. He would be unable to sleep the night before or to retain food the morning he was to appear in court. Prior to the start of the trial he frequently asked for a brief delay, by one excuse or another, and slipped out to the washroom and vomited. Then he found that a drink of whisky was a great help in controlling his apprehension.

In the meantime he married a girl who was socially prominent from a family that was financially secure. She was more aggressive sexually than the patient and before the honeymoon was over he was impotent. This he attributed to alcohol, but he continued to drink. Six years later he was literally dashing home at the end of the day for a drink. Once home he quickly drank himself into a stupor. Sometimes he ate dinner but, as often as not, he just drank.

However, he still scrupulously adhered to the pattern of not drinking in the morning or during the day unless he was to appear in court. He was convinced that as long as he was able to avoid a morning drink and to appear for work, he was not an alcoholic. His practice increased during this interval in spite of his drinking. It was not until his seventh year in practice that he began to drink during the day. During this same year, he was first hospitalized after a bout.

This patient's law practice and his marriage evolved along with his alcoholism. As he said, he would "never have had the nerve" to propose to his wife had he been sober. It was no surprise that, when his wife demanded that he either stop drinking or she would sue for a divorce, he continued to drink. The same choice was made when his friends attempted to persuade him to give up drinking because it was ruining his practice. Eventually his secretary and his acquaintances attempted to conceal his condition and to meet his obligations when he was too stuporous to carry on his work. He responded by drinking all the more.

Treatment

The treatment of alcoholism may be divided into two phases: the correction of the reversible physiological changes which follow a prolonged excessive intake of alcohol; and the prevention of a resumption of the drinking.

Treatment of Acute Effects of Alcohol

The major advances in treatment have been in the first phase. Mortality statistics in uncomplicated alcoholic delirium are not available for the last quarter of a century. However, they are undoubtedly much lower than the 37 per cent reported for the period prior to that time. This improvement has not resulted from psychi-

atric insight or better whisky but from improved medical care and the use of antibiotics.

The changes that have occurred in the management of delirium reflect the nonspecific nature of some of the approaches to this illness. In 1915 Steinbach (1), in Germany, published a paper on the treatment of this condition by spinal drainage. His recommendation was based on a postulated cerebral edema caused by a "toxin." This happened to be the era when "toxins" were prevalent, and the idea was widely accepted. But Steinbach not only advocated spinal drainage, he also recommended the replacement of the fluid with normal saline to dilute the "toxin."

This replacement tended to complicate a difficult procedure and most clinicians settled for a spinal tap, as "toxins" were replaced by "viruses." In addition to the spinal drainage, which is not always easily done in an actively delirious patient, fluids were withheld, the patient was purged, and hypertonic solutions were given intravenously. It should be noted that in spite of the effort required to immobilize a disturbed patient in order to obtain a determination of his spinal fluid pressure, this procedure was carried out in 211 delirious alcoholics, and in 73 per cent the pressure was normal.

Two decades later, Piker (2) and Bowman, Wortis and Keiser (3), advocated hydrating rather than dehydrating these patients and the alcoholics cooperated by surviving in greater numbers. The greatest decrease in mortality, however, has occurred in the patients whose delirium was complicated by pneumonia, a fracture or other injuries.

A second area of improved management in the treatment of acute effects of alcohol has occurred since the introduction of the phenothiazine derivatives and the skeletal muscle relaxants (the so-called major and minor tranquilizers). The patient apparently does not have a cross-tolerance for these compounds as he does for the barbiturates, and relief is obtained without giving a toxic dose.

Ideally, a drug used to control alcoholic delirium or delirium from any other cause would have the following properties: effectiveness and rapidity of action, anticonvulsant activity and a minimum of untoward side effects. It would not create psychic or physiological dependence nor aggravate existing pathology. According to recent reports, chlordiazepoxide[2] meets most of these criteria.

[2] Librium, Hoffmann–La Roche, Inc.

Factors in Sobriety

The second phase is literally the treatment of the sober alcoholic.

In an attempt to clarify what factors provoke a resumption of drinking after an interval of abstinence, 62 alcoholics were studied, of whom 44 were outpatients seen privately and 18 were male alcoholics committed to a state hospital.

The reasons for drinking most frequently given by the outpatients were the usual rationalizations: "I drink like everybody else;" or "I wanted a drink and I took it;" or "a nagging wife;" or "I just got fed up." Several patients replied to the question by saying, "I wish I knew." Perhaps an insightful answer was given by a female patient, who first said she didn't know why she drank and then added, "I guess it's because of my husband." When asked what he did that provoked her to drink, she replied, "He doesn't do anything, he's just too damned dull to endure sober."

Such responses offer little insight into what prompts a resumption of the drinking. However, the following factors were evident in the outpatient group: the nature of the event which preceded the drinking, whether it made the patient happy, morose or angry, was not nearly as important as the time at which it occurred in the interval of sobriety. The alcoholic would tolerate a nagging wife or an inconsiderate employer for 6 weeks or 2 months, or whatever was his usual period of abstinence and then drink because of his wife or employer. In other words, these patients had fixed patterns of sobriety as well as of drinking (4, 5). Some averaged a bout three or four times a year; others rarely went more than 3 weeks or a month without taking a drink.

Characteristically, the patients made no effort while sober to alter the irritations which eventually provoked their drinking. Usually the outpatient's family and his employer were involved in this pattern of sobriety, i.e., they anticipated the patient's alcoholic bouts and were frequently able to predict when the patient would drink.

As a group the outpatients were still responsive to the demands of their families or employers; their abstinence was frequently the result of a threat of the loss of one or the other of these supports. In contrast, 12 of the 18 committed patients no longer had direct family ties, all had repeatedly lost jobs because of their drinking, and in essence, they were without the restraints of responsibility. In the committed patients, therefore, the greatest force for sobriety was a controlled environment. In fact, the committed patient seemed

to respond directly to his environment: if the environment prevented drinking, he adjusted quite readily and easily to the imposed sobriety; on the other hand, if drinking was practiced and permitted, he just as readily drank.

The outpatients were concerned over such complications of their drinking as arrests for drunkenness, blackouts, grand mal seizures, or delirium following a bout. On the other hand, all but 3 of the committed group reported that they had experienced blackouts for several years while drinking; and several had undergone episodes of delirium on one or more occasions. All but 3 of the committed patients had been arrested from 1 to 14 times for drunkenness.

From the evidence seen in these patients it appears that in the beginning of his alcoholic career the individual is influenced to abstain by the consequence of his drinking. After a variable period of excess (usually 2 to 5 years) he evolves a pattern of intermittent sobriety which avoids conscious consideration of the problem. This change is evidenced by the patient's refusal to discuss his drinking when sober, denial of the difficulties his excess has created or, later on, his histrionic protests that since he admits he is an alcoholic, there is no need to discuss his recent drunken behavior—since he plans to drink no more.

As the patient's alcoholism becomes more disruptive and his illness more obvious, the influence of the bout on his intervals of sobriety becomes more marked and more lasting. He becomes known as an alcoholic. He is no longer able to terminate a bout and continue his previous behavior pattern as though nothing had happened. His family and employer become increasingly involved and the patient's pattern of sobriety develops as an attempted compromise between two persisting demands—his inner needs which are temporarily relieved by alcohol and the external requirements of responsibility.

The more responsive the alcoholic is to these external pressures, the longer he can maintain whatever position he had achieved (maritally, professionally or socially) before his drinking prevented further success. The greater the inner need for alcohol, the more rapidly the pattern of sobriety disintegrates, and the earlier the destructive effects of the drinking become evident.

Treatment during Abstinence

It appears essential to make the patient aware of the pattern of sobriety that he is following. He should be prepared for an interval of increased tension at the time he usually drinks after a period of abstinence. During this particularly vulnerable interval he should be seen frequently by his physician and be given a medication for relief of tension if he is anxious.

It should also be pointed out to the patient that he may consciously or unconsciously plan to drink after the usual abstinent interval. He should be told that he will undoubtedly find sufficient reasons to justify the first drink; he will feel that his having avoided drinking justifies it.

On the other hand, the physician must recall that alcoholism is above all else a chronic illness and that the drinking and nondrinking behavior has become habitual. Friends, routine and impulse all tend to prolong the disease. Therefore, if the patient slips once or twice while making that very difficult transition to sobriety, the physician should not be excessively discouraged.

Summary

Various problems in treating the alcoholic are discussed, including factors inhibiting the acceptance of the diagnosis and of treatment, the role of drinking in the alcoholic's life, advances in the treatment of acute effects of alcohol, factors influencing abstinence, and treatment during abstinence.

REFERENCES

1. Steinbach, R. Ueber die Zerebrospinalflüssigkeit und über die Wirkung der Lumbalpunktion beim Delirium potatorum. Dtsch. med. Wschr. **41**: 369–372, 1915.
2. Piker, P. On the relationship of the sudden withdrawal of alcohol to delirium tremens. Amer. J. Psychiat. **93**: 1387–1390, 1937.
3. Bowman, K. M., Wortis, H. and Keiser, S. The treatment of delirium tremens. J. Amer. med. Ass. **112**: 1217–1219, 1939.
4. Smith, J. A. Psychiatry: Descriptive and Dynamic. Baltimore; Williams & Wilkins; 1960.
5. Smith, J. A., Herrick, H. and Rudy, L. H. Patterns of sobriety in the alcoholic. Dis. nerv. Syst. **21**: 622–625, 1960.

The Use of Pharmacological Adjuncts in the Psychotherapy of Alcoholics

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CLINICAL EXPERIENCE makes it clear that alcoholics constitute a mixed group of ill people suffering from a complex of psychological, social, spiritual and metabolic disturbances or maladaptations. Furthermore, although the symptom of pathological use of alcohol is common to all of them, they show varied patterns of drinking, loss of control and changes in tolerance. An important objective of therapeutic research is to categorize these patients according to the disturbances they exhibit and the patterns of their alcoholism so as to provide data for exploring etiological factors. A problem still facing the therapist stems from his inability to plan therapy based upon a confident theory of etiology. It may well be that therapeutic research, particularly research emphasizing a comprehensive approach to the patient and his family in a community setting, will uncover etiologically based therapeutic regimens. However, an effective method of treatment—conceivably in the field of psychopharmacology—may be found even before insight into etiology has been gained.

The present paper is a report of three studies evaluating pharmacological or metabolic adjuncts in the outpatient therapy of alcoholics. The first reviews the use of disulfiram as a measure to enforce motivation for abstinence. The second is a study of adjuncts to correct hypothesized metabolic defects. The third and most detailed deals with attempts to protect the alcoholic patient against the effects of abnormal autonomic activity generated by presumedly disordered cerebral autonomic control mechanisms.

Sample and Procedure

The subjects in the studies reported here were all treated at the facilities of the Division of Alcohol Studies and Rehabilitation of the

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Commonwealth of Virginia. Patients were first seen by a member of the therapeutic team in one of nine outpatient clinics distributed throughout the state. Most of them were initiated into therapy by a period of hospitalization, lasting for approximately a week, in the specialized service for alcoholics at the Medical College of Virginia in Richmond. Over 50 per cent of the patients admitted to this hospital facility are completely sober on admission; the others are intoxicated or show alcohol withdrawal symptoms. Relatively few are admitted while deeply intoxicated or exhibiting delirium tremens, hallucinosis, convulsions or other serious acute manifestations. The period of hospitalization was followed by prolonged treatment in the hospital's outpatient clinic. Patients, therefore, were necessarily selected from those capable of accepting therapy on a so-called voluntary basis.

While the patient was in the hospital a detailed medical and psychological study was made as well as a study by a social worker of the patient and his family, where this seemed indicated. Warm friendly relations between the staff and the patient were part of the therapeutic setting. There were never more than 12 patients on the ward at any one time. Both men and women were accepted. Therapy in small groups was begun the first day, since most patients were out of bed during the day from the time of admission. The objectives of group therapy were to give information, to stimulate motivation and to encourage group interaction. While in the hospital each patient was seen one or more times by the physician who later followed him in the outpatient clinic.

While the patients under study fell into a variety of diagnostic categories requiring specific therapeutic planning, certain characteristics were common to nearly all of them. A majority suffered from feelings of worthlessness which acted to paralyze effective action, and virtually all were the victims of family and community ignorance and misinformation about alcoholism and tended to have unrealistic ideas about the nature of their own problems and possible means of recovery. The motivation for rehabilitation of such patients can be broadened and strengthened by the assurance of the therapist's acceptance of them as worthwhile people whose lives are valuable. It is easy for them to see themselves as worthless and inevitably condemned to deterioration.

Disulfiram

Disulfiram has been used for alcoholics in various ways. One method is to build a "pharmacological fence" around the patient and so to transfer from him to the drug the responsibility for abstinence. In our experience, this has not been a successful procedure. Actually, the alcoholic can never permanently delegate to any other person or modality the privilege and responsibility of his own de-

cision about abstaining. In our use of disulfiram,[2] the patient was encouraged to take the drug each day, only after he had, in the quiet of his own room, specifically reexperienced his acceptance of the fact that he could not drink and had chosen to accept another day of abstinence. He then took the medication unsupervised and was free from any further decision about the matter until the next day at the same time. If the patient had any doubts about his acceptance of his alcoholism or his wish to undertake another day of sobriety, he was counseled not to take the disulfiram but to contact his clinic physician.

An analysis of 1,020 patients at the Medical College of Virginia who took disulfiram and 484 controls (1) revealed that the disulfiram-treated patients constituted a younger group than the controls, the peak of the former being in the 35–39 age group and that of the controls in the 40–44 age group. Apparently, in our setting, disulfiram was selected by a younger, healthier, more highly motivated group and rejected by or denied to older patients with more profound deterioration. Only 55 per cent of the controls benefited from treatment, whereas 76 per cent of the disulfiram-treated patients improved. The disulfiram group stayed in treatment significantly longer; only 1 per cent broke treatment early (by self-discharge from the hospital) compared to 17 per cent of the controls. In the disulfiram group 77 per cent of the males and 67 per cent of the females improved. Those in the disulfiram group who were between the ages of 40 and 44 made the best clinical progress.

These studies showed that under the conditions of our therapeutic setting the disulfiram group as a whole does better than the controls. It is of interest to note that this difference also showed up among the patients who established a pattern of sobriety only after one or more drinking relapses. It was hypothesized that disulfiram is selected by those more highly motivated patients who will continue long-term treatment more faithfully. Additional incentive for continuation of treatment may have been provided by the fact that the disulfiram was dispensed in the clinic itself at the time the patient saw the clinic doctor and only enough of the medication was given to last until the next appointment. The motivation hypothesis was evaluated statistically excluding those patients from both the disulfiram and control groups who broke

[2] Antabuse, Ayerst.

treatment by self-discharge from the hospital and who were lost to contact. In the resulting comparison of 928 disulfiram-treated patients with 333 controls, it was found that 84 per cent of the disulfiram group were listed as improved while 80 per cent of the controls were so classified, a difference which is not clearly significant. In an earlier study, Hoff and McKeown (2) found that those controls who volunteered for disulfiram but were denied it had much better records than those who declined it. Of 69 patients who were denied disulfiram on physical or psychological grounds, none discontinued treatment early and 62 per cent improved. Of 152 patients who declined the medication, 31 per cent discontinued treatment early and only 44 per cent improved. The group denied disulfiram were apparently a more highly motivated group who may have accepted the condition which disqualified them as a challenge to find a new way of life.

Adjuncts to Correct Metabolic Defects

Massive Polyvitamin Supplementation

This metabolic approach to the treatment of alcoholics stems from studies of Williams (3) who found that rats receiving a marginal diet select high alcohol intake and who has reported cases of alcoholics in whom the compulsion to drink was presumably lost when they were given specific vitamin supplements.

In 1955 Hoff and Forbes (4) reported a study of 100 patients from our clinic which was designed to explore the effects of long-term administration of a polyvitamin formula on the drinking patterns of alcoholics. During their 7-day hospital stay the patients received daily oral doses of 100 mg. of ascorbic acid plus 15 cc. of a polyvitamin formula. Each 5-cc. dose of the formula contained 5 mg. of thiamine hydrochloride, 2 mg. of riboflavin, 10 mg. of niacinamide, 10 mg. of panthenol, 2 mg. of pyridoxine hydrochloride, 10 mg. of *p*-aminobenzoic acid, 500 mg. of choline dihydrochloride, 100 mg. of inositol, 100 mg. of methionine, and 5 mg. of vitamin B_{12}. After discharge they were maintained with 10 cc. of the formula plus 100 mg. of ascorbic acid daily for at least a year.

The sample comprised all those admitted to the hospital service during a 3-month period. The progress of these patients was compared with that of 100 control patients admitted consecutively during a later 3-month period. All patients in both series were non-

psychotic alcoholics accepted on a voluntary basis and subjected to an otherwise identical therapeutic regimen. The patients in the control series received vitamins during the hospitalization period but none subsequently. All the patients were evaluated 1, 2 and 3 years after the onset of treatment.

In general, the statistical analysis suggested that the differences in clinical success (i.e., abstinence and family, job and social adjustment) between the groups could be explained by random variation. It was evident, however, on a clinical basis that patients in the vitamin group felt better and ate better than those in the control group and subsequent experience with this formula has shown that it is a valuable adjunct in helping outpatients cope with anorexia and excessive fatigue. No patient in any of our series has ever acquired any degree of control over the use of alcohol whether taking vitamins or not.

One problem with any experiment involving administration of drugs or other agents to outpatients is that there is always some doubt as to whether or not the patient took the medication. This can be checked absolutely only by assigning to a member of the family or some other responsible person the task of supervising the administration. As has been implied in the case of disulfiram, such a procedure tends to defeat the underlying principle on which the adjunctive use of the medication is based. It is our impression, however, that disulfiram is taken according to the physician's suggestions more consistently than is a vitamin preparation. Patient acceptance of chlordiazepoxide (to be discussed below) appears to us to be even greater than disulfiram although, as will be seen, the rationale of its use is different.

Enzyme Deficiency

It has been suggested that individual genetic differences in enzyme activity may affect alcohol metabolism and conceivably play a part in the etiology of alcoholism (5). Wilson and Respess (6) found that C57BL/6J mice prefer alcohol to water and show a higher level of liver alcohol dehydrogenase than do C3H control mice. Furthermore, the former animals, under conditions in which an alcohol solution is the only source of liquid, will accept and use greater amounts of alcohol than will the controls. Such studies, while not yet clinically applicable, suggest a promising therapeutic research approach.

Adjuncts to Correct Hormonal Defects

Many studies support the hypothesis that alcoholism, while not a clear-cut single disease entity, may be causally related in part to hormonal imbalance. Many alcoholics relate their drinking to feelings of nervousness or tension or depression that may stem from tension. Hoffer and Osmond (7) have suggested that alcoholics and other tense people either may not synthesize enough adrenochrome or may destroy it too quickly. Alcohol as a tension-dissolving substance may be used as a substitute for this missing adrenochrome. Alcoholics and those with chronic tension states have been found to lose injected adrenochrome from plasma much more quickly than normal subjects. Hoffer and Payza (8), comparing the adrenochrome levels in the cerebrospinal fluid and in plasma, found that very tense patients had a lower ratio of cerebrospinal fluid adrenochrome to plasma adrenochrome than those who are not tense. Jantz (9) reported that serum from alcoholics metabolized adrenochrome to adrenolutin more quickly than did normal serum. Hoffer and Osmond offer the view that chronically tense people are more likely to become alcoholics than those who are not. Fleetwood (10) has shown that alcoholics have more sympathomimetic amines in their red cells and plasma when they are tense than when they are relaxed or have ingested alcohol.

The hypothesis that abnormal tension in alcoholics is based on a physiological peculiarity is potentially useful in treating alcoholics. It can help relieve some of their guilt and self-reproach. Furthermore, the administration of adrenochrome, substitutes for adrenochrome, or substances which aid in its synthesis or delay its breakdown may be beneficial.

At the Medical College of Virginia preliminary trials with the administration of leuco-adrenochrome (by sublingual absorption in amounts of 15 mg. four times a day) have recently been effective in abolishing tremor in three tense, tremulous patients all of whom had complained of tremor, especially under emotional stress, most of their lives.

Protection against Autonomic Overactivity

Effects of Chlordiazepoxide[8] *and of Alcohol*

Several studies (11–14) have established the existence, both in experimental animals and in man, of cortical and subcortical repre-

[8] Librium, Hoffmann–La Roche, Inc.

sentation of visceral control. Specifically, stimulation of isocortical, paleocortical and other cerebral areas results in alteration of systemic blood pressure, changes in intracardiac dynamics and modifications of peripheral circulation as well as functional and vascular changes in the kidneys, gut and other organs. Acute and chronic changes in pulmonary, coronary and bone marrow circulation have been investigated and it has been shown that cortical stimulation modifies activity of epinephrine and norepinephrine as well as salivation. It may be hypothesized that there is an overlapping and integration of cortical–visceral and somatic control systems and that these systems are related to neurological mechanisms of behavior and emotional response. Tension and emotional sensitivity and lability, of whatever origin, may be related at the neurological level to disturbances of these higher cerebral autonomic mechanisms. Neurotropic drugs, therefore, which protect the autonomic system from higher cerebral overresponse to stresses may be of value as adjuncts in the therapy of alcoholics.

Recently, Carroll et al. (15) have compared the action of intravenously administered alcohol and chlordiazepoxide on autonomic responses evoked in cats by threshold stimulation (with controlled parameters) of isocortical loci and loci in the limbic lobe, the amygdala, the nucleus of von Bechterew, the hypothalamus and the mesencephalic reticular formation. Unipolar stimulation, through electrodes stereotaxically placed in flaxedilized cats, evoked pressor responses, cardiac arrhythmias (nodal and ventricular extrasystoles and ventricular tachycardia with indications of coronary insufficiency), mydriasis and striking inhibition of the motility of the pyloric sphincter and ileum. Salivation has also been elicited from most of these loci as well as retraction of the nictitating membrane. Intravenous administration of chlordiazepoxide in amounts of 10 to 20 mg. per kg. of body weight caused a transient, slight hypotension and bradycardia whereas intravenous administration of 10-per-cent ethanol (3 to 15 ml. per kg., leading to blood alcohol levels of 0.05 to 0.15 mg. per 100 ml.) caused increased pyloric motility with slight to marked alterations in cardiac rhythm. Chlordiazepoxide greatly attenuated the pressor responses from all brain areas studied whereas alcohol generally exerted weak antipressor effects. Centrally induced cardiac arrhythmias were completely blocked by chlordiazepoxide but alcohol had no blocking action on these responses except from loci in the limbic lobe. Neither

compound showed any activity against centrally evoked salivation, mydriasis or gastrointestinal inhibition.

Alcohol, as measured by its effects upon centrally induced autonomic responses, appears to be a defective tranquilizing agent. In fact, its central actions on higher brain functions seem to be a complicated combination of excitatory and inhibitory effects. Whereas alcohol is an imperfect attenuator of centrally generated autonomic overactivity, chlordiazepoxide acts effectively to protect the viscera from harmful cerebral autonomic malfunction.

Chlordiazepoxide as a Treatment Adjunct

Because chlordiazepoxide fulfills criteria of an effective neuropharmacological substance with protective action, as measured by its suppression of cerebrally induced visceral malfunctions, a study was carried out to evaluate its use as an adjunct in the long-term treatment of a group of 100 alcoholics. Fifty patients (40 men, 10 women) received 10 to 25 mg. of chlordiazepoxide orally four times a day both during the hospital stay and after discharge. The first patient in this series was admitted on 1 May 1960 and the last on 10 February 1961. Their ages ranged from 28 to 63. Fifty patients, matched with the chlordiazepoxide patients in age, sex and time of entry into the hospital, served as controls. The controls received no special placebo; in the hospital they were given capsules of B-complex when the other patients received chlordiazepoxide. All were followed up to the time of the present report. The results of this study can be seen in Table 1. It may be reasonably assumed that Classes *IV*, *NC*, and *NT* represent, for the most part, therapeutic failures.

According to the criteria for degree of abstinence, 72 per cent of the chlordiazepoxide-treated patients improved, 10 per cent did not and 18 per cent could not be classified. In contrast, 52 per cent of the control patients improved, 16 per cent did not, 24 per cent were lost to contact and 8 per cent discontinued treatment early. The chlordiazepoxide-treated group shows a significant improvement over the control group (chi square=4.24; $P<.05$).

According to the less stringent criteria, based on symptomatic improvement, in the lower portion of Table 1, 82 per cent of the chlordiazepoxide-treated patients were improved, 14 per cent unimproved and 4 per cent unclassified. Of the control patients, 60 per cent were improved, 20 per cent unimproved, and 20 per cent

TABLE 1.—*Comparisons of Degree of Abstinence and of Symptomatic Improvement in 50 Patients Treated with Chlordiazepoxide and in 50 Controls (in Per Cent)*

DEGREE OF ABSTINENCE*	CHLORDIAZEPOXIDE	CONTROLS
I	20	16
II	8	10
III	36	26
IV	10	16
V	8	0
NC	18	8
NT	0	24
SYMPTOMATIC IMPROVEMENT†		
1	22	16
2	22	18
3	38	26
4	14	20
0	4	20

* The criteria for classification were as follows. I: Patients reporting total abstinence since the onset of treatment. II: Patients abstinent except for one relapse. III: Patients not abstinent but showing improvement in wider spacing of drinking episodes, better work records and happier adjustments in home and community. IV: Patients showing no improvement. V: Patients placed in the unimproved class in earlier appraisals, who have been continuously abstinent for over 6 months. NC: Patients with whom contact was lost. NT: Patients who discontinued treatment early through self-discharge or other means.

† The criteria for classification were as follows: 1: Vast improvement or nearly complete remission of all symptoms. 2: Decided improvement or partial remission of symptoms. 3: Slight improvement. 4: Condition unchanged or worse. 0: Could not be classified.

could not be classified. This difference in improvement is also significant (chi square=5.88; $P<.05$). It should be noted that in the chlordiazepoxide group, fewer patients withdrew from the series or were unclassifiable than in the control group. There was a higher follow-up rate in the chlordiazepoxide group and fewer missed appointments.

In no patient in this series was administration of chlordiazepoxide associated with any manifestation of toxicity. A special group of 10 of the chlordiazepoxide patients were rehospitalized 6 months after the onset of therapy. Medical and psychological tests were repeated in these patients but they revealed no toxic changes. These retest studies will be reported in detail in a subsequent paper.

Patients taking chlordiazepoxide showed greater willingness and ability to explore and face personality problems and life situations than did the controls. There was a tendency towards breakdown of alibi systems and a facing of reality. The chlordiazepoxide-treated patients were also more tolerant of job and family problems and better able to handle these situations. They showed less overt

tension and slept and ate better. The troublesome symptoms of some, such as palpitations, epigastric discomfort, pain and tremulousness, were greatly abated and finally abolished. The chlordiazepoxide-treated patients showed a notable willingness to go beyond relief of immediate tension and overt symptoms and to seek insight. Some of these points are illustrated in the following case summaries:

Case 1.—This 38-year-old married white woman came to the clinic with a history of a progressively severe spree-drinking problem during the previous 8 years. Prior efforts to maintain abstinence had been ineffectual, no period of sobriety having lasted longer than 8 weeks. Her 15-year-old son, who showed behavior problems, was under supervision by a county social worker. The younger son, 13 years old, suffered from a congenital heart condition. Medical and laboratory examinations of the patient were within normal limits. The woman was depressed and felt that she had reached a dead-end with her husband and family. Their house was dilapidated and lacked plumbing and the patient had no incentive to care for it. She was revealed in the psychological tests as a sensitive, somewhat immature and egocentric person with average intellectual ability, confronted by situational difficulties for which she felt there was no solution.

This patient received chlordiazepoxide (10 mg. four times daily) from the beginning of hospitalization. She has missed only one appointment from the onset of outpatient treatment in May 1960 to the time of writing. She and her husband moved to a newly-built house in an attractive neighborhood. She secured a part-time job for herself. She also showed interest in providing attractive clothes for herself and her family and began to attend church and Alcoholics Anonymous. This patient has remained abstinent in spite of continuing problems with her two children. Rehospitalization in February 1961 brought to light no untoward effects of the medication and the psychological protocol indicated improved adjustment and greater acceptance of the emotional challenges of her environment, with less tension and less desire or need to act out her tensions and frustrations in an explosive manner.

Case 2.—This 45-year-old self-employed building contractor was a social drinker for 25 years. For 2 years before treatment began he had been consuming between a pint and a fifth of whisky daily. It appeared that he drank to relieve tension. Medical and laboratory examinations were essentially normal. The psychological tests revealed the patient as a somewhat immature, self-centered individual of average intellectual ability who was capable of making a satisfactory adjustment. Guilt feelings associated with recent actions as well as a close dependent relationship with the mother-figure and a conflict with the father-figure were indicated. He was able to sleep only 3 to 4 hours a night.

This patient received chlordiazepoxide in the hospital and four to eight 10-mg. capsules of the medication each day after discharge. He remained abstinent from the onset of therapy in June 1960 to the time of writing, with the exception of 2 days' drinking in November 1960. In the course of outpatient therapy the patient felt progressively less depressed and began to sleep well. He asserted that while in the past he had made snap decisions, he was beginning to think things over carefully before acting. His work became more efficient and his financial situation improved greatly. He felt that the drug "brought him down to earth" and enhanced his ability to think things through. After his relapse in November he felt guilty and expressed a need for more effectual dealing with his problems. He began to discuss his family situation in more detail and achieved a better adjustment with his wife. Rehospitalization in February 1961 showed no medical abnormalities. The psychological tests indicated that he was more anxious than in the previous July but the anxiety was of the introspective kind. To the extent to which introspection was necessary for the development of insight it seemed that his adjustment was better at the time of readmission than at the onset of therapy. The patient had become more concerned about his own behavior in relation to the environment. His thinking was more self-evaluative and he showed a tendency to stand aside and judge his own actions, sometimes unfavorably, in relation to the behavior of others.

Case 3.—This 31-year-old married salesman was admitted with a history of increasingly severe spree-drinking during the previous 5 years. He drank whenever a crisis developed or when he became anxious or depressed. He said that he used alcohol to relieve tension and anxiety, to help in business deals and to prevent marital friction. There was a complicated history of family discord. Examination revealed gastritis and a duodenal deformity with the probability of an active duodenal ulcer. Psychological examination showed the patient to be an obsessive–compulsive psychoneurotic with overwhelming feelings of inner tension, anxiety and insecurity. His derisive self-evaluative tendency seemed to cripple his initiative and prevent him from functioning at his optimal level of intellectual efficiency. An inadequate acceptance of his own masculine identity and difficulty in the area of interpersonal relationships were prominent in the record.

This patient was accepted for therapy in May 1960 and attended the outpatient clinic up to the time of the present report. He took chlordiazepoxide from the beginning and gradually increased his dosage to 100 mg. daily. In January 1961 he was rehospitalized for evaluation. At that time the physical and laboratory studies revealed no abnormality. There were no side effects attributable to the drug. In the psychological tests the obsessive–compulsive defenses were still outstanding and his tendency to compare himself unfavorably with others and to engage in excessive self-evaluation persisted. His anxiety had been lowered but

he seemed unable to maintain his earlier front of bravado, jest and condescension toward others and showed some tendency toward withdrawal. The test findings indicated that with therapy he was becoming better able to understand his underlying feelings of inadequacy and his depression and fear. At the beginning of 1961 the patient's area of business suffered a serious recession and he was unable to keep his income at its previous level, apparently through no fault of his own. In spite of this and the situational problems associated with finding other work, the patient has remained abstinent.

Summary

Various pharmacological adjuncts to the treatment of alcoholics that have been used with patients at the Medical College of Virginia are discussed. Subjects were treated initially as inpatients for 7 days while medical, psychological and, in some instances, social casework studies, were made. After discharge they continued in treatment as outpatients, with regular interviews with a physician at the clinic.

Disulfiram was used as a treatment adjunct to enforce motivation in a group of 1,020 subjects with 484 controls. The percentages of each group that benefited from treatment were 76 and 55 respectively. Disulfiram-treated patients stayed in treatment longer. It is suggested that patients willing to take this drug are more highly motivated than others.

Massive polyvitamin supplementation was studied in 100 subjects and 100 controls. While no significant differences in abstinence or family, job or social adjustment were evident, this treatment was valuable in combating anorexia and excessive fatigue.

It is suggested that therapeutic approaches based on restoring enzyme deficiencies may be found useful in the future.

The possible usefulness of drugs such as leuco-adrenochrome to correct hormonal imbalances resulting in abnormal tension is discussed.

Comparative effects of alcohol and chlordiazepoxide on cerebral processes affecting autonomic activity are discussed.

Chlordiazepoxide proved an effective adjunct to treatment in a study of 100 patients of whom half were used as controls. Subjects received 10 to 25 mg. of the drug orally 4 times a day both during the hospital stay and after discharge. They were followed for periods of 3 months to 1 year. Using degree of abstinence as the criteria, 72 per cent of the chlordiazepoxide-treated patients and

52 per cent of the controls improved to some extent. Using symptomatic improvement as the criteria, 82 per cent of the drug-treated patients and 60 per cent of the controls improved to some extent. No harmful side effects were seen in the drug patients. Three brief case histories are given.

REFERENCES

1. Hoff, E. C. The use of disulfiram (Antabuse) in the comprehensive therapy of a group of 1,020 alcoholics. Conn. St. med. J. 19: 793–797, 1955.
2. Hoff, E. C. and McKeown, C. E. An evaluation of the use of tetraethylthiuram disulfide in the treatment of 560 cases of alcohol addiction. Amer. J. Psychiat. 109: 670–673, 1953.
3. Williams, R. J. Alcoholism as a nutritional problem. J. clin. Nutrit. 1: 32–36, 1952.
4. Hoff, E. C. and Forbes, J. C. Some effects of alcohol on metabolic mechanisms, with applications to therapy of alcoholics. In: Sevag, M. G., Reid, R. D. and Reynolds, O. E., eds. Origins of Resistance to Toxic Agents; pp. 184–193. New York; Academic Press; 1955.
5. Hoff, E. C. The etiology of alcoholism. Quart. J. Stud. Alc., Suppl. No. 1, pp. 57–65, 1961.
6. Wilson, E. C. and Respess, J. C. A study of ethanol metabolism in mice which preferentially consume ethanol. Gastroenterology [in press].
7. Hoffer, A. and Osmond, H. Concerning an etiological factor in alcoholism. The possible role of adrenochrome metabolism. Quart. J. Stud. Alc. 20: 750–756, 1959.
8. Hoffer, A. and Payza, A. Adrenochrome levels in plasma and cerebrospinal fluid. [Presented at the Annual Meeting, American Psychiatric Association, San Francisco, 1958.]
9. Jantz, H. Über Stoffwechseluntersuchungen bei Alkoholpsychosen. Zbl. ges. Neurol. Psychiat. 137: 141–142, 1958.
10. Fleetwood, M. F. Biochemical experimental investigations of emotions and chronic alcoholism. In: Diethelm, O., ed. Etiology of Chronic Alcoholism; pp. 43–109. Springfield, Ill.; Thomas; 1955.
11. Hoff, E. C. and Green, H. D. Cardiovascular reactions induced by electrical stimulation of the cerebral cortex. Amer. J. Physiol. 117: 411–422, 1936.
12. Green, H. D. and Hoff, E. C. Effects of faradic stimulation of the cerebral cortex on limb and renal volumes in the cat and monkey. Amer. J. Physiol. 118: 641–658, 1937.
13. Hoff, E. C., Kell, J. F., Jr., Hastings, N., Sholes, D. M. and Gray, E. H. Vasomotor, cellular and functional changes produced in kidney by brain stimulation. J. Neurophysiol. 14: 317–332, 1951.
14. Ferguson, R. W., Folkow, B., Mitts, M. G. and Hoff, E. C. Effect of cortical stimulation upon epinephrine activity. J. Neurophysiol. 20: 329–339, 1957.
15. Carroll, M. N., Jr., Hoff, E. C., Kell, J. F., Jr. and Suter, C. G. The effects of ethanol and chlordiazepoxide in altering autonomic responses evoked by isocortical and paleocortical stimulation. Biochem. Pharmacol. 8: 15, 1961.

A Report of a Rehabilitation Program for Alcoholic Women Prisoners

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THIS REPORT deals with clinical experience during the first two years (1958–1960) of a pilot project for the rehabilitation of alcoholic women prisoners from the Massachusetts Correctional Institution in Framingham. The project was jointly sponsored by the Alcoholic Clinic of the Peter Bent Brigham Hospital in Boston, the Massachusetts Correctional Institution, the Massachusetts Division of Alcoholism and the Massachusetts Division of Legal Medicine.

From its inception the keystone of this rehabilitation program has been the establishment of a continuous therapeutic relationship between the therapist and the alcoholic woman. The greatest emphasis has been placed on having the same therapist treat the alcoholic both during her prison stay and after her release into the community. A 1955 Massachusetts law made it mandatory that alcoholics from State prisons be referred to a medical clinic for follow-up care. The intent of this law reflects a genuine concern for the welfare of these men and women and a belief that their problem is a medical one. However, in the 3 years prior to the program described in this report, despite the fact that thousands of men and women were so referred, only a handful reported to their assigned alcoholic clinic.

The project described here was designed to carry out the intent of the legislation. With this in mind our clinic set itself two goals: (*a*) to determine whether continuous relationship therapy can lead to a successful transfer of the alcoholic woman from the custody

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of the prison to treatment at the alcoholic clinic; and (*b*) to determine the extent to which medical facilities can be beneficial. The second goal raises the further question of whether the rehabilitation of alcoholic prisoners should be assigned to medical establishments even when these alcoholics do not naturally consider these facilities as their usual source of help. In view of the gravity of the alcoholic's physical, social and psychiatric problems, the goals considered in the present study are obviously conservative. The results are discussed only in terms of the value of this steady relationship with a psychiatrically oriented person and of the ability of medical and psychiatric facilities to help these unstable women weather the serious crises that repeatedly arise in their lives.

Women Alcoholics at the Massachusetts Correctional Institution

Several studies have been made of the extent of alcohol problems among the women at this institution. One survey[5] of the records of the first 100 admissions in 1955 revealed that 32 of these women had been sentenced for drunkenness. All of these had had previous court appearances. Total arrests for the group were 723—an average of 23 arrests per woman. Following their imprisonment in 1955, 22 had subsequent court records and 2 suffered violent deaths. Over the next 5 years, these 22 women were arrested 224 times, averaging 10 arrests per woman. In 1958 another survey[6] of 100 consecutive admissions showed that 53 of the women had been sentenced for drunkenness. Of the remaining 47 admissions, 17 women who were imprisoned for offenses other than drunkenness showed evidence of severe drinking. Both these surveys, as well as the authors' own clinical experience, indicate that alcoholism constitutes the major problem of this particular institution.

In a report of a previous clinical study[7] the psychiatric picture of the alcoholic women in this institution was discussed. Manifestations of the primitive nature of their orally fixed drives were seen in the early onset of their addiction, their sexual perversions and their extreme dependency needs. These disturbances were usually reflected either in the people they chose as homosexual or heterosexual partners or in the manner in which they related

[5] MYERSON, D. J. and NEIBERG, N. Unpublished data.

[6] CRAMER, J. and BLACKER, E. Unpublished data.

[7] MYERSON, D. J. Clinical observation on a group of alcoholic prisoners. With special reference to women. Quart. J. Stud. Alc. **20**: 555–572, 1959.

in the psychotherapeutic situation. As sexual partners they chose people like themselves with the result that the relationship was characterized by domination and submission, sadomasochistic perversions and such exorbitant demands that one partner or the other eventually deserted. In the therapeutic relationship their demands on the therapists, whether implicit or explicit, eventually created a situation in which the therapists were forced either to act out with their patients or to frustrate them. Whether deserted or frustrated, their reactions were characteristic and immediate—dangerous drinking, self-destructive promiscuity or, among the most disturbed, violent rage reactions.

Their failures to adapt to the usual community requirements began early, as indicated by consistently poor school and work records, and continued with histories of multiple marriages, illegitimate pregnancies, the loss of children to the State, or homosexuality. By the time that their social failures brought these women to the courts there was, because of their destitution, isolation and dangerous drinking patterns, no alternative but to sentence them to the prison. It was not just a question of their amorality, but actually of their survival.

Diagnostically these women resemble sociopaths. Judging from their total failure to adapt to society and their turbulent reactions to slight frustrations, they certainly can be categorized among the most disturbed of the alcoholic groups.

Sample

From August 1958 to September 1960, 49 women from 18 to 55 years old were treated. The majority were in their mid-thirties; 30 were Roman Catholics and 19 Protestants. All were native-born. All recounted early and extreme emotional deprivations as indicated by stories of parental cruelties, divorces, desertions and deaths. Histories of parental alcoholism and early sexual seduction were examples of the disorganization of the family structure.

Most of the women had left school at about the eighth or ninth grades; 5 had finished high school. With the exception of 1 nurse, all were unskilled workers with records of extreme instability. Ten of the women were active homosexuals; 13 were single; 21 were either divorced, separated or deserted; 9 had a history of multiple marriages. This group of 49 women had produced 15 illegitimate and 34 legitimate children, the vast majority of whom received State support and care.

At the time of commitment all were destitute. The offenses cited for this particular commitment were: drunkenness in 21 cases; drugs, 3;

neglect of minor children, 7; idle and disorderly conduct (prostitution), 7; lewd and lascivious conduct, 4; manslaughter, 2; stubborn child, 1; forgery, 1; assault and battery, 1; and voluntary commitment, 2.

Procedure

The project utilized the services of two psychiatric social workers from the Alcoholic Clinic of the Peter Bent Brigham Hospital under the supervision of its clinical director. Each worker spent an afternoon each week at the Massachusetts Correctional Institution and consulted with four to five women. The time spent with each woman varied from 10 to 45 minutes depending on her emotional reaction. Although the therapists, out of respect to the vulnerability of these women, tended to keep the interview neutral, it was not unusual to note rage reactions, depressions or episodes of overeating afterward. When such reactions were observed the therapists shortened the time of the next interview.

After release from prison, therapy was generally supportive, consisting chiefly of the use of medical facilities to meet the various crises in the alcoholic's life in the community. These facilities included the hospital's outpatient department and its emergency ward which could admit patients for overnight care. If more inpatient time was necessary the therapists utilized the facilities of other medical institutions such as the Boston State Hospital or the Boston City Hospital. For a few women a medically operated "half-way house," connected with the psychiatric ward of the Boston City Hospital, was available. In addition, the therapist offered a series of interviews, conducted in a sympathetic professional atmosphere in which the alcoholics could discuss their problems. Some of the problems most commonly discussed concerned relationships with husbands, parents, children and homosexual partners.

For a variety of reasons women were selected for this program on a haphazard basis. In general, women over 45 or those whose homes were too far from Boston to commute to the clinic were eliminated. The program was completely voluntary. A woman might refuse to continue her visits, even in the prison. On the other hand, there is no doubt that preference was given to those who expressed interest. The extremes of absolute refusal or strong desire for help were rare. For the most part, the women were assigned to the program by the prison staff whenever the therapist's appointment time was open. Even those who complied as though it were a prison regulation did seem to appreciate the visits and there is no question that they trusted the therapists.

Results

Results were tabulated in accordance with the original aims of the project: to determine the value of continuous relationship therapy in the transfer from prison custody to clinic treatment; and to determine how beneficial medical facilities were for these

women. In terms of results the women may be divided into four groups:

1. Twenty women never appeared at the clinic after discharge from the prison. Of these, 15 were seen in the first year and 5 in the second. This difference seems to indicate that the program achieved greater acceptance as it continued. Of these 20 women, 6 were returned to prison within a year of their discharge.

2. Eighteen women continued the therapeutic relationship or used the facilities of the hospital for their therapeutic advantage: Eight of these reported for the treatment of phobias; 12 for a drinking crisis. All of them discussed various family problems and 3 brought their husbands into the clinic for aid in the treatment. Two women used the hospital for specific medical and surgical procedures other than the routine physical examination. All these cases were considered successful in the sense that the women used either the therapeutic relationship or the hospital facilities to their advantage.

3. Seven women came to the clinic for help but in spite of treatment using every available medical facility they began to drink in an uncontrolled way as soon as they were released from the various institutions. They were not brought under control until they were finally incarcerated at the prison. Of these women, four were addicted to drugs as well as alcohol. One, a 19-year-old girl, could be considered psychotic on the basis of her extreme rage reaction to the slightest frustration. Even in prison, control of this girl was finally achieved only through use of a "strong room."

4. Four women reported to the clinic and did well, but did not use the therapist or the clinic in any demonstrable advantageous way. They made sporadic visits but only because they apparently thought it was compulsory. Little was learned about them. Certainly they never turned to the clinic in a crisis. Either they adjusted well on their own or, if they had difficulties, their families or friends were able to sustain them.

Discussion and Conclusions

One area where the therapists provided considerable support centered about the alcoholics' reactions to separation from the prison and readjustment in the community. In the initial phases of therapy the women generally idealized their coming freedom

and minimized the separation problem. If therapy was successful, however, more anxiety was expressed as the time for departure drew nearer. Finally, when departure from prison occurred, most of the women complained of moderate phobic reactions. With eight such women the treatment of the phobic reaction became the central problem following discharge.

There were certain important limitations of the program, some of which became evident when the women left prison. The therapist worked on an appointment basis and within the confines of the hospital clinic. It was therefore the alcoholic's responsibility to get to the clinic if she needed emergency care. Unfortunately, the alcoholic usually needs help at inconvenient times and in places far from a clinic. Further, the therapist had no authority to enforce any decision. Finally, there were distinct limits to the facilities of the hospital, which is relatively small. The project could not interfere with the other varied responsibilities of this institution. It operated chiefly as an outpatient service and had to rely on other hospitals for longer stays when necessary.

The most important drawback, however, involved the therapeutic relationship itself. If the therapist tries to satisfy the unlimited needs of the alcoholic, the relationship becomes one of acting out and can be disastrous to both participants unless the therapist has unlimited energy. If the therapist maintains limits, the situation leads to a conflict and becomes another frustrating experience for the alcoholic who then tends to discharge her anger in a characteristically destructive way. It is difficult to predict in individual cases whether an alcoholic can be helped to withstand this frustration and accept certain limits without drinking or other destructive action; or, if she does react to the frustration, whether she will accept the help of the clinic to control her subsequent drinking.

This problem within the confines of the therapeutic relationship represents the essence of the struggle these women have with the community. Just as the community expects its members to live within certain limits so must the therapist set limits for his patients. The difference lies in the professional therapeutic approach of the latter as opposed to the traditionally punitive and restrictive approach of the former.

With reference to the first goal of the study, the clinical experience showed that sustained therapeutic relationships are ef-

fective in aiding the transfer from the prison to the clinic. Whereas prior to this program no women reported to the clinic, even though they had received instructions to do so, during the period studied 29 out of 49 reported. It is believed that this proportion will grow with continued operation of the project.

As for the second aim, the results indicated that the psychiatric and medical approach had value for these women since 18 of them benefited directly. Given the nature of their disturbance, however, it is clear that the medical approach alone is not enough, even though it is generally conceded that these people are sick. It is interesting to note that the State Hospital, which is the only hospital system that can offer complete incarceration, cannot or does not generally wish to handle such impulsive women.

Of the seven women who could not be controlled, at least none were killed or engaged in promiscuous sexual behavior during their bouts of drinking, and they knew where to turn for help. These women represent a group that probably needs indefinite commitment. From this clinical experience, it seems highly unlikely that any of them can make a successful adjustment.

It would appear that the ultimate development of this rehabilitation program will require a combination of the best in hospital and in prison facilities.

Summary

This report describes an attempt to rehabilitate alcoholic women prisoners by providing a continuous relationship with one therapist before and after their release from prison. Two psychiatric social workers held weekly interviews with the alcoholics before their release from prison and were available after release for interviews by appointment at a hospital clinic where medical facilities were also provided. Of 49 women, 20 left treatment on release from prison; 18 benefited either from the postrelease interviews or from the clinic's medical facilities; 7 continued the interviews but also continued their uncontrolled drinking until they were reincarcerated; and 4 visited the clinic sporadically and improved but their improvement could not be attributed to the clinic therapy. It is concluded that sustained therapeutic relationships do contribute to a successful transfer from prison custody to clinic treatment and that a medical–psychiatric approach to treatment is of value but should be supplemented by other approaches.

Special Announcement

Yale Center of Alcohol Studies to Become Rutgers University Center of Alcohol Studies

The Center of Alcohol Studies which had its beginnings at Yale University a generation ago will be relocated at Rutgers, The State University of New Jersey, as the Rutgers Center of Alcohol Studies. Formal announcement of the move was made by Dr. Mason W. Gross, President of Rutgers, at New Brunswick, New Jersey, on 6 October 1961. The establishment of the Center of Alcohol Studies at Rutgers will be aided by a grant of $927,000 from the National Institute of Mental Health to cover the basic budget of the Center for the next 6 years. It is expected that the process of transferring the Center from New Haven to New Brunswick will be substantially completed during the first half of 1962.

In a public statement welcoming the Center of Alcohol Studies to Rutgers, Doctor Gross noted that "the Center's research and extension activities on behalf of greater knowledge and understanding of social problems are fully in keeping with the educational and research activities of New Jersey's State University. We believe that by welcoming these students of the problems involving alcohol, Rutgers can perform an increasingly important and valuable service not only for New Jersey, but for the entire nation. The problems arising from the use of alcohol are complex and difficult to solve. Our efforts to solve them through this new Center will go closely in hand with what Rutgers is trying to do in its new Urban Studies Center, namely, to delve deeply into the complicated problems of our intense urban life."

Doctor Gross also pointed out that the Summer School of Alcohol Studies, which gained a national reputation at Yale, will be held at Rutgers beginning in 1962, where it will form a "practical and logical addition" to the State University's extensive summer program in such fields as human relations, banking, labor education, and the upgrading of elementary and secondary school teachers. He noted, further, that the announcement of the establishment of the Rutgers Center of Alcohol Studies followed by only two months the announcement of the University's new medical school program, and that valuable interrelationships of the two new activities at Rutgers are anticipated both in research and teaching. Plans for transfer of the Center from Yale provide for appointments to the Rutgers staff for all the "core" personnel of the Center.

The principal functions of the Rutgers Center, as outlined by Doctor Gross, will include:

1. Research into various problems involving the use of alcohol—physiological, psychological, sociological, and economic.
2. Teaching of groups with a special interest in problems of alcohol. This will be done in a summer program, the Yale counterpart of which has been nationally famous for years.
3. Documentation of all forms of study dealing with alcohol.
4. Publication and dissemination of materials dealing with the subject, including the QUARTERLY JOURNAL OF STUDIES ON ALCOHOL.

Correspondence: Correspondents of the Center of Alcohol Studies, the Summer School of Alcohol Studies, the Classified Abstract Archive of the Alcohol Literature, the Alcoholism Treatment Digest, and the Publications Division are advised to continue to use the present address (52 Hillhouse Ave., Yale University, New Haven, Connecticut) until further notice. Subscriptions and other business correspondence, as well as editorial communications to the QUARTERLY JOURNAL OF STUDIES ON ALCOHOL, should likewise be addressed as heretofore (2162 Yale Station, New Haven, Connecticut).

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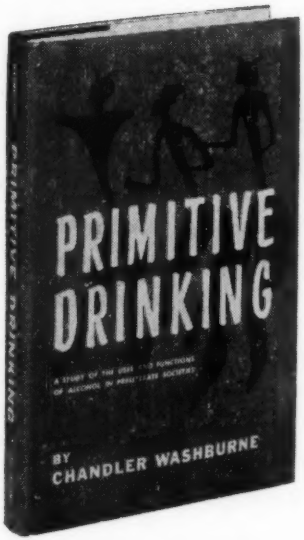

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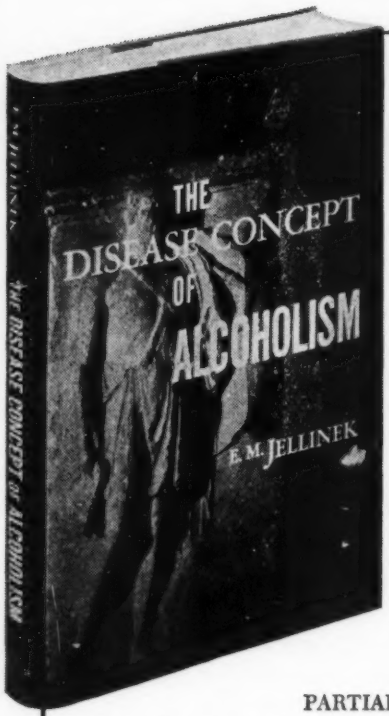

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